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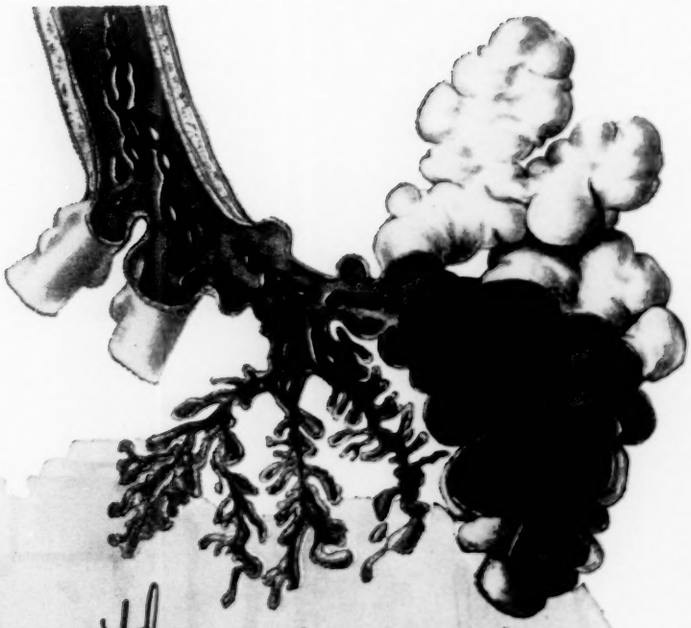
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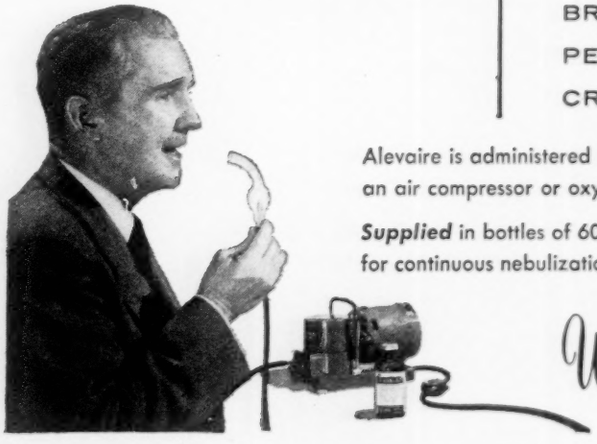
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The American Journal of Medicine

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Clinical Studies

A General Theory of the Causes of Murmurs in the Cardiovascular System
DAVID L. BRUNS 360

Dr. Bruns makes a brilliant contribution to theories of the causation of cardiac murmurs. He begins by reviewing the evidence for current views based on turbulence of blood flow and/or "cavitation" bubbles, and points out their inadequacies. He argues that acoustical energy in murmurs is for the most part due to periodic fluctuations in the downstream wake of any obstacle, and that the characteristics of this type of flow are similar to those associated with Aeolian tones or orifice flow. It is suggested that most murmurs are due to protuberances, discontinuities in the surfaces of the heart valves and the larger vessels, and are intensified by relatively small increases in blood flow. The theoretical basis of the general theory is supported by experimental evidence in the form of models and experiments in dogs.

Angina Pectoris. I. A Variant Form of Angina Pectoris. Preliminary Report
MYRON PRINZMETAL, REXFORD KENNAMER, REUBEN MERLISS, TAKASHI WADA AND NACI BOR 375

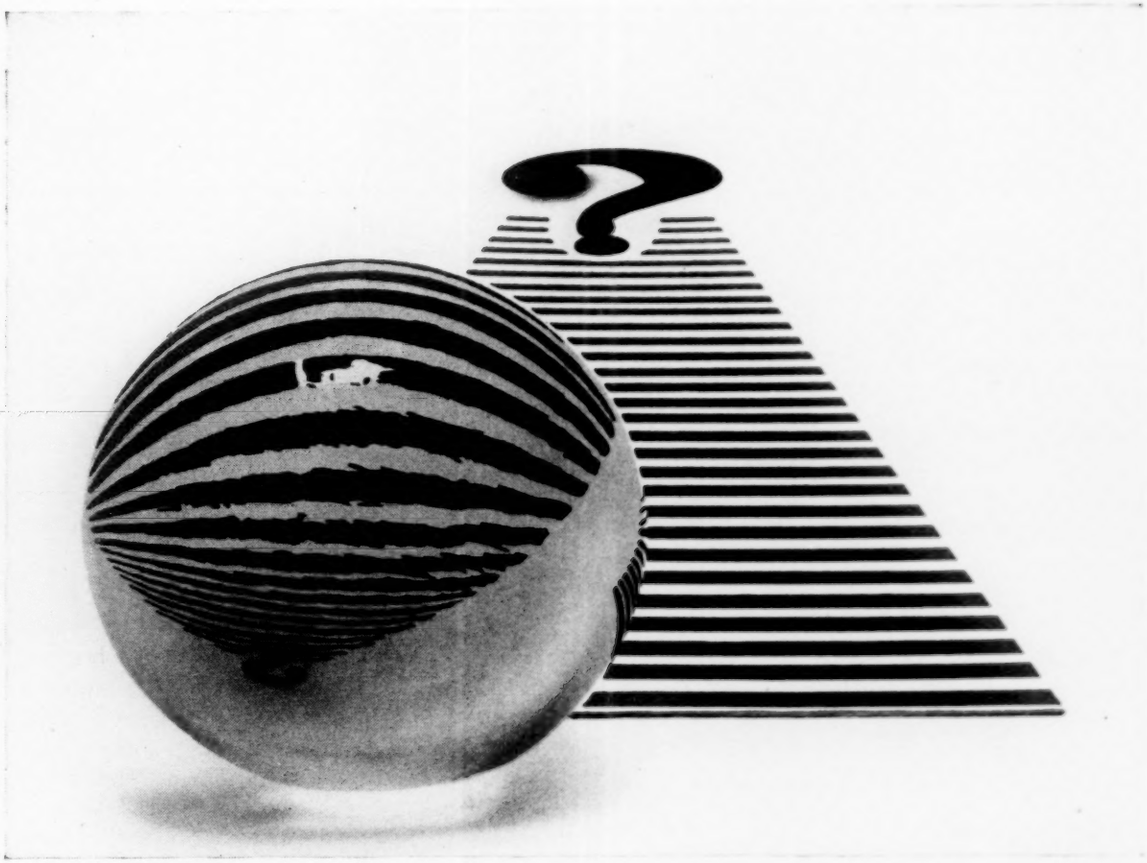
Dr. Prinzmetal and his collaborators focus attention upon an interesting variant of angina pectoris which appears to be associated with temporary, recurrent spasm of a partially occluded coronary artery. In contrast to the usual angina pectoris, precordial pain in this variant is apt to come on at rest and is relieved by exercise. There is a striking elevation of the ST segment during severe attacks of pain, simulating myocardial infarction, but this promptly reverts to normal upon cessation of the attack.

Paroxysmal Nocturnal Hemoglobinuria. I. Clinical Studies
ROBERT C. HARTMANN AND JOSEPH V. AUDITORE 389

Paroxysmal Nocturnal Hemoglobinuria. II. Erythrocyte Acetylcholinesterase Defect . . . . . JOSEPH V. AUDITORE AND ROBERT C. HARTMANN 401

Apart from the fact that the abnormality in paroxysmal nocturnal hemoglobinuria resides in the red cell and not in the blood plasma, little has been discovered about the defect responsible for this curious malady. The present study describes a characteristic decrease in erythrocyte stromal acetylcholinesterase activity which may provide a clue to pathogenesis. The first paper gives an interesting and informative account of six cases of paroxysmal nocturnal hemoglobinuria, bringing

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what lurks beyond the broad spectrum?

"Broad spectrum" has evolved into an especially apt term to describe a growing number of "specialized" antibiotics. These provide the best means of destroying pathogenic bacteria which range all the way from large protozoa through gram-negative and gram-positive bacteria to certain viruses at the far end of the spectrum.

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out some features which have not hitherto been stressed. The second paper describes, in convincing detail, the nature and extent of the defective erythrocyte acetylcholinesterase activity in this disorder, and makes it plain that this defect in erythrocyte enzymes is fairly characteristic of paroxysmal nocturnal hemoglobinuria alone. It is not yet possible to offer a precise explanation of how the enzyme deficiency brings about the hemolytic manifestations of the disease.

A Comparative Study of Four Prothrombinopenic Anticoagulant Drugs. I. Properties
THEODORE RODMAN, CHARLES S. RYAN AND BERNARD H. PASTOR, WITH THE TECHNICAL ASSISTANCE OF ESTHER HARRISON 411

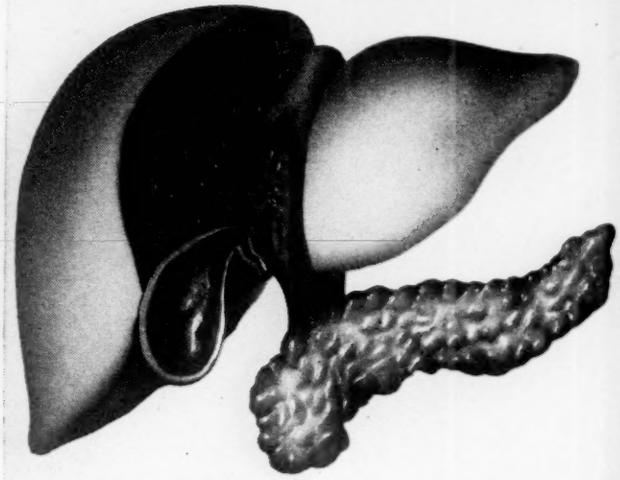
A Comparative Study of Four Prothrombinopenic Anticoagulant Drugs. II. Clinical Study
THEODORE RODMAN, CHARLES S. RYAN, BERNARD H. PASTOR AND WERNER J. HOLLENDONNER, WITH THE TECHNICAL ASSISTANCE OF ESTHER HARRISON 415

So many claims and counterclaims have been made for special advantages of the several prothrombinopenic anticoagulant drugs available that an objective comparative study such as this is welcome. The investigators used bishydroxycoumarin (dicumarol), warfarin (prothromadin), phenindione (Hedulin®) and diphenadione (Dipaxin®). In the first orientating study of onset, peak activity and duration of effects of these drugs, the chief difference was found to be in duration of effect, presumably reflecting varying rates of excretion and metabolic degradation of the drugs. In the second study, conducted in patients with diseases ordinarily treated with anticoagulants, the drugs were compared with an eye to details of management. Satisfactory control of prothrombin activity could be achieved with all four drugs, but somewhat more readily with bishydroxycoumarin and diphenadione, which also tended to elicit somewhat more stable responses. All four drugs may cause hemorrhage, of course, and all four have the serious defect, at least in such disorders as myocardial infarction, of many hours of delay in achieving a therapeutic range of depression of prothrombin activity (unlike heparin). It is suggested that, as is the practice with many other drugs, anticoagulant therapy be initiated with a large single loading dose of the drug employed, followed by smaller maintenance doses; this program did not seem to carry more risk of hemorrhage than the conventional induction schedule.

Comparison of Chlorambucil and Myleran in Chronic Lymphocytic and Granulocytic Leukemia
R. W. RUNDLES, JAMES GRIZZLE, WARREN N. BELL, C. C. CORLEY, W. B. FROMMEYER, JR., B. G. GREENBERG, C. M. HUGULEY, JR., G. WATSON JAMES, III, RALPH JONES, JR., WILLIAM E. LARSEN, VIRGIL LOEB, L. A. LEONE, J. G. PALMER, W. H. RISER, JR. AND S. J. WILSON 424

In a well designed if rather brief study, it was clearly demonstrated that chlorambucil usually is more effective than Myleran® in the treatment of chronic lymphocytic leukemia, and less likely to produce incidental thrombocytopenia; whereas Myleran is distinctly more effective than chlor-

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why should the urine be tested for sugar in acute cholecystitis?

The high incidence of pancreatic disease associated with pathologic conditions of the biliary tract indicates their close relationship. The appearance of glycosuria in acute cholecystitis points to involvement of the pancreas in the inflammatory process.

Source: Refresher Article: Biliary Tract Diseases, M. Times *85*:1081, 1957.

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ambucil in the treatment of chronic granulocytic leukemia. The analysis of results brought out a number of additional points of interest both as to the practical management of the chronic leukemias, and more general considerations of the development of new oncolytic agents. Not the least relevant point illustrated is the demonstration once again of the value of cooperative study groups in carrying out valid therapeutic assays of important new drugs.

Pseudoxanthoma Elasticum. A Systemic Disorder
MASON G. ROBERTSON AND J. SPALDING SCHRODER 433

It is worth emphasizing again, as this report does, that pseudoxanthoma elasticum is a systemic disorder not limited to the characteristic abnormalities of the elastic tissue of the skin (which may indeed be inconspicuous) and of the retina (angioid streaks) but also involving vessels throughout the body. On this account there may be hemorrhage from the gastrointestinal tract and other sites, and premature medial calcification of blood vessels with coronary, cerebral and peripheral vascular insufficiency.

D-Xylose and Its Use in the Diagnosis of Malabsorptive States
PHILIP A. CHRISTIANSEN, JOSEPH B. KIRSNER AND JEAN ABLAZA 443

The absorption of the pentose, d-xylose, has been suggested as a measure of intestinal absorptive rates in general, and carbohydrate absorption in particular. The present study evaluates the usefulness of this test in the diagnosis of malabsorptive states. After studies in a variety of other intestinal disorders (as an indication of specificity) and comparisons with plasma carotene, fat absorption and glucose tolerance tests (as an indication of sensitivity) it is concluded that the d-xylose test is perhaps the most useful procedure available for screening cases of malabsorption syndrome.

Review

Rheumatism and Psoriasis. A Re-evaluation . . . . . V. WRIGHT 454

While there are still some skeptics, the consensus is that a distinct form of arthropathy may occur in association with psoriasis. This view is supported by the present study which defines psoriatic arthritis as an entity characterized by psoriasis and erosive arthritis, with a negative Rose-Waaler differential agglutination test. Analysis of a large series of patients fulfilling these criteria has led the author to distinguish three subgroups of this disorder: psoriatic arthritis involving chiefly the distal interphalangeal joints, with typical skin and nail changes (i.e., the usual form of psoriatic arthropathy); severe deforming arthritis, which may progress to the stage of arthritis mutilans; and arthritis clinically indistinguishable from rheumatoid arthritis.

Seminar on Mycotic Infections

Aspergillosis. A Review and Report of Twelve Cases
SYDNEY M. FINEGOLD, DRAKE WILL AND JOHN F. MURRAY 463

Twelve cases of probable or established aspergillosis are recorded, in eleven of which the fungal infection was implanted upon a debilitating disease (neoplasm, leukemia) after prolonged treat-

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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: Am. J. M. Sc. *234*:150, Aug. 1957. 2. Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Am. J. M. Sc. *233*:280, March 1957. 3. Boyd, L. J., Huppert, V. F., Mulinos, M. G. and Hammer, H.: Am. J. Cardiol. *3*:229, Feb. 1959.

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ment with antibiotics and/or steroids. This sequence of events, secondary fungal infection, is reported with increasing frequency, and presents a growing therapeutic problem. In the case of aspergillosis, early recognition is difficult and no effective therapy is available as yet.

Clinicopathologic Conference

"Adult" Mucoviscidosis 483

Clinicopathologic Conference (Washington University School of Medicine)

Case Reports

Chronic Cor Pulmonale Due to Multiple Pulmonary Emboli and Accompanied by Diffuse Interstitial Fibrosis
STEPHEN B. LANGFELD, F. THOMAS HOPKINS AND EDWARD A. THEURKAUF, JR. 494

A well studied case.

Dissecting Aneurysm of the Aorta Treated Surgically
ELI H. RUBIN, MORRIS RUBIN AND BERNARD SEIDENBERG 501

This interesting case is an example of modern surgical attempts to treat dissecting aneurysm of the aorta. The problems in diagnosis are discussed and the surgical experience with this condition is completely reviewed.

So-called Primary Ulcerohypertrophic Ileocecal Tuberculosis
F. F. PAUSTIAN AND H. L. BOCKUS 509

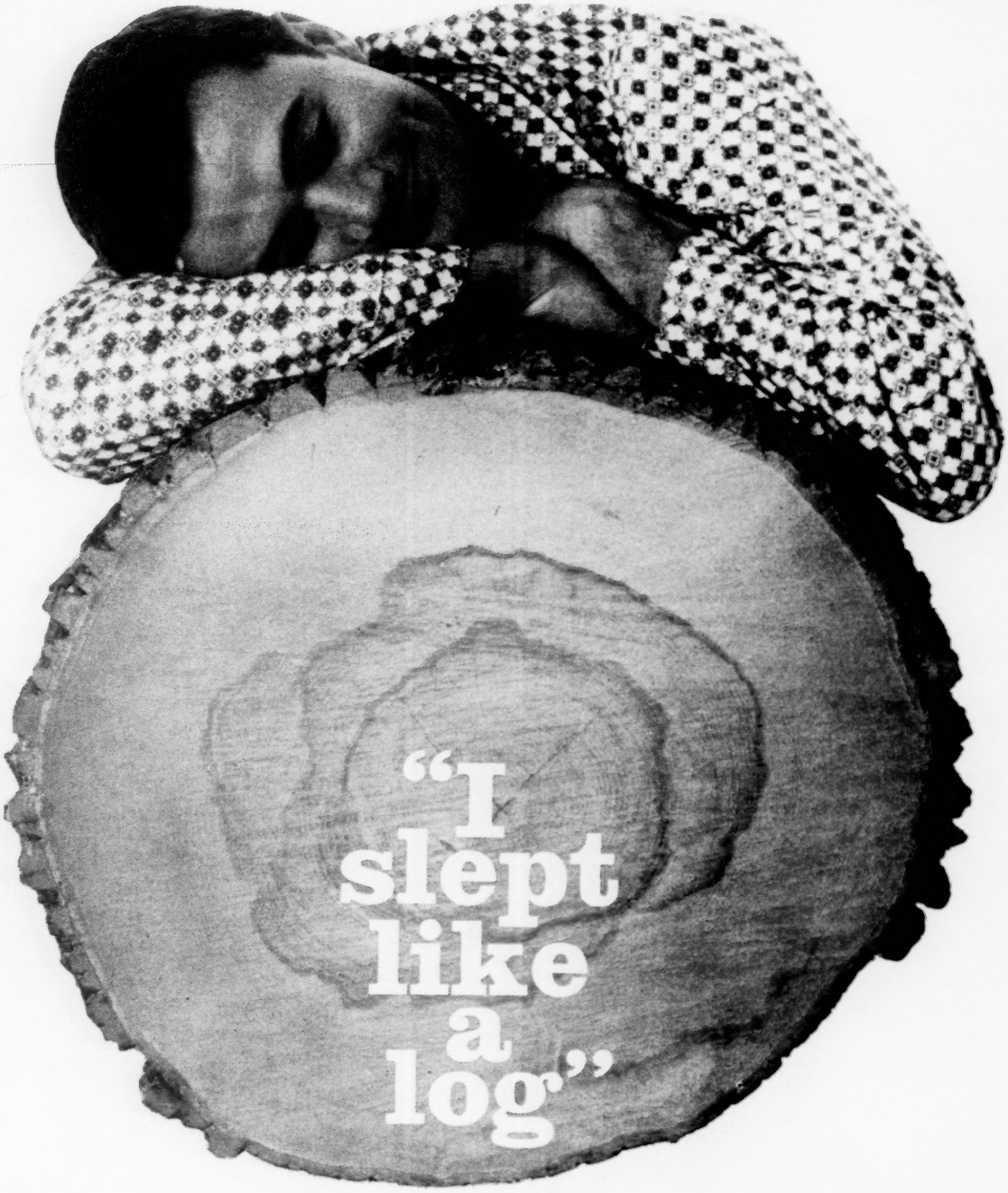
An informative discussion of this now uncommon lesion, with a well studied case.

Demecolcine Toxicity. A Case Report of Severe Hematopoietic Toxicity and a Review of the Literature . . . WILLIAM A. DITTMAN AND JOHN R. WARD 519

A patient with acute gouty arthritis inadvertently received an overdose of demecolcine, and promptly demonstrated severe toxic effects. These may occur, however, even with ordinary dosage.

Advertising Index on Page 151

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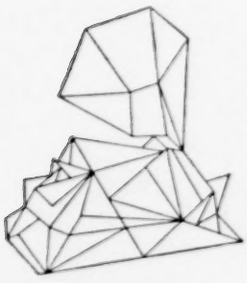
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References: (1) Gould, A. H. and Long, D. L.: Clinical Pharmacology and Therapeutic Use of Dexbrompheniramine Maleate (Disomer), a new Histamine Antagonist (submitted for publication). (2) Medical Department, White Laboratories, Inc.

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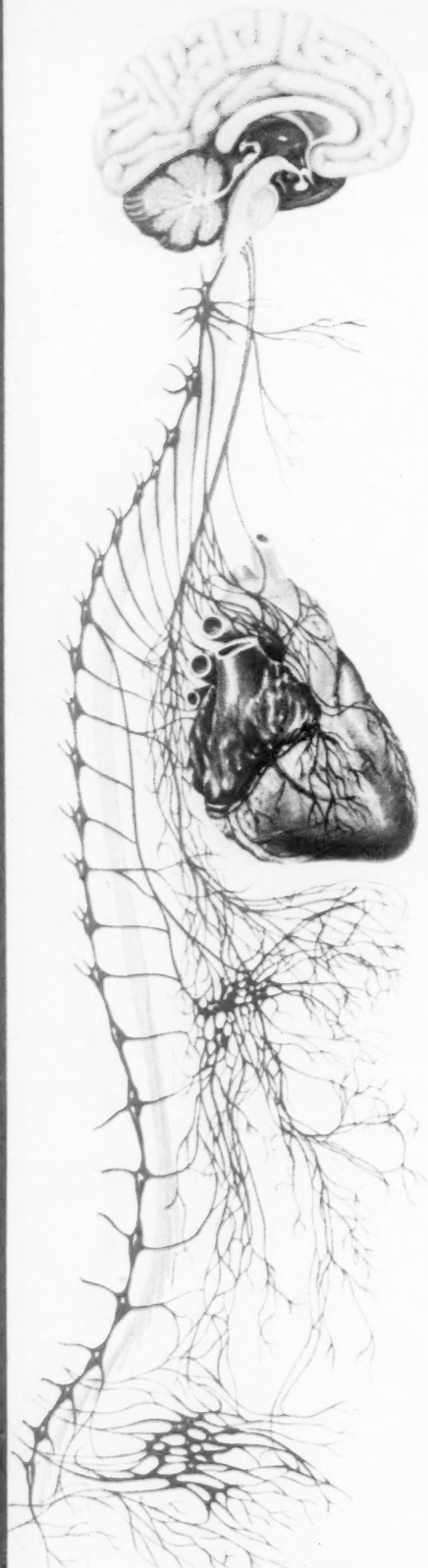


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RESULTS OF "DOUBLE-BLIND" STUDY OF 99 MIXED ANXIETY AND TENSION PATIENTS[1]

Side Effects	Tablet A Deserpidine 43 patients	Tablet C Placebo 24 patients	Tablet C Reserpine 27 patients
DIZZINESS	0 (0%)	3 (12%)	4 (15%)
DRYNESS OF MOUTH	3 (7%)	1 (4%)	6 (22%)
BIZARRE DREAMS	0 (0%)	2 (8%)	7 (26%)
LISTLESSNESS	1 (2%)	4 (17%)	9 (33%)
DETACHMENT (Diminished awareness)	0 (0%)	0 (0%)	2 (7%)
ANOREXIA	1 (2%)	3 (12%)	4 (15%)
WEAKNESS, TIREDNESS, NO PEP	0 (0%)	8 (33%)	16 (59%)
DAYTIME SLEEPINESS	1 (2%)	4 (17%)	19 (70%)
HEADACHE	0 (0%)	18 (75%)	4 (15%)
NAUSEA	0 (0%)	2 (8%)	3 (11%)
ABDOMINAL CRAMPS	1 (2%)	4 (17%)	5 (18%)
RASH	0 (0%)	0 (0%)	0 (0%)
NASAL STUFFINESS	1 (2%)	0 (0%)	4 (15%)
LOOSE STOOLS	0 (0%)	1 (4%)	3 (11%)

Percentages supplied by Abbott Laboratories.

Author's Comments: "With deserpidine there was less abrupt hypotensive action on blood pressure than with reserpine, and less fatigue or sleepiness during the day."

COMPARISON OF SIDE EFFECTS IN 80 HYPERTENSIVES TREATED WITH VARIOUS FORMS OF RAUWOLFIA[2]

Side Effects	Reserpine	Alseroxylon	Deserpidine	Rescinnamine
LETHARGY	11	10	1	1
NASAL OBSTRUCTION	10	8	8	2
DREAMS	8	7	3	1
ACHING	8	7	3	0
DEPRESSION	3	3	0	1
DIARRHEA	2	3	1	0

Author's Comments: "Deserpidine when given in the morning, showed a definitely lower incidence of lethargy, and depression was not encountered in any patient."

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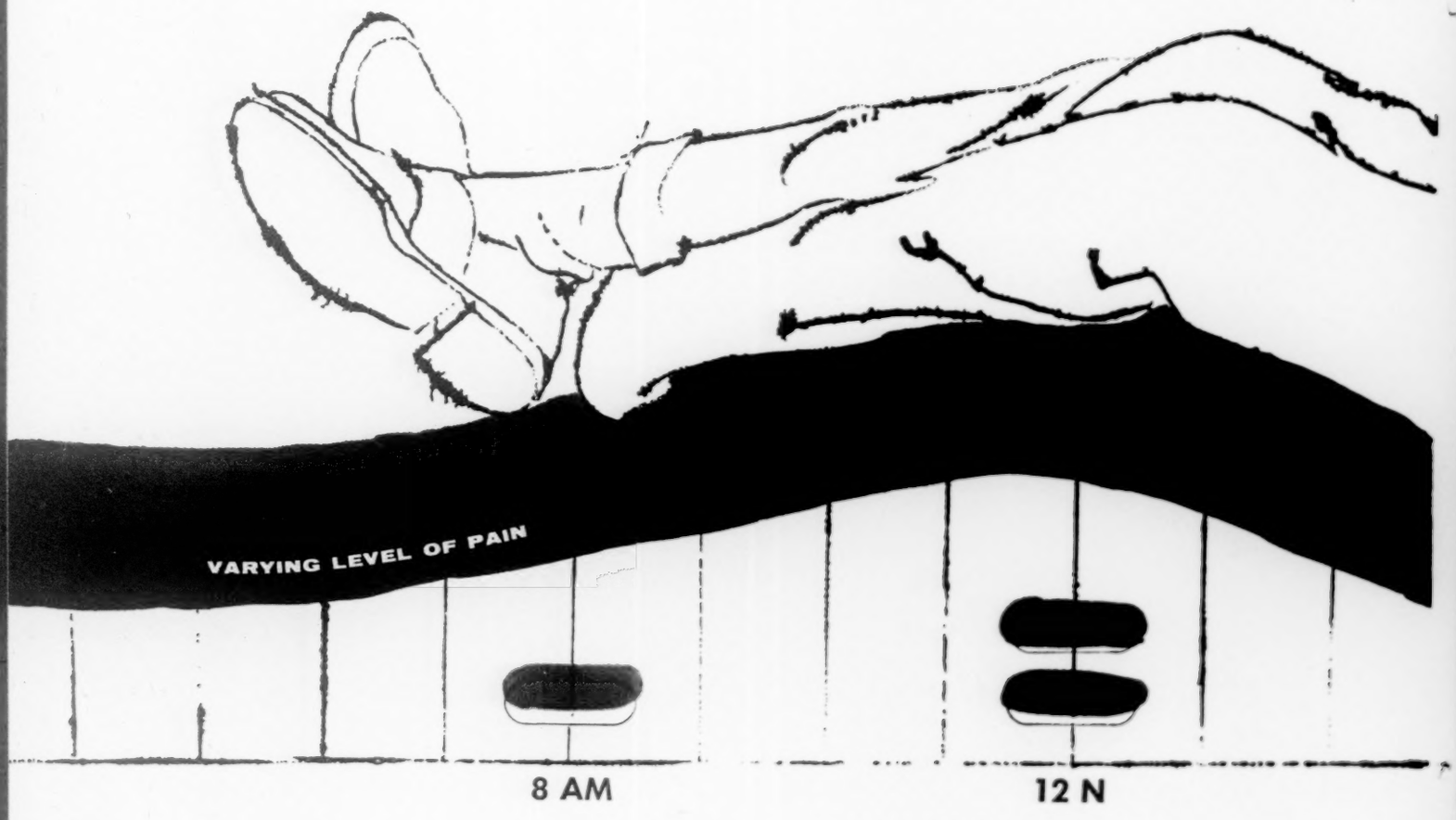
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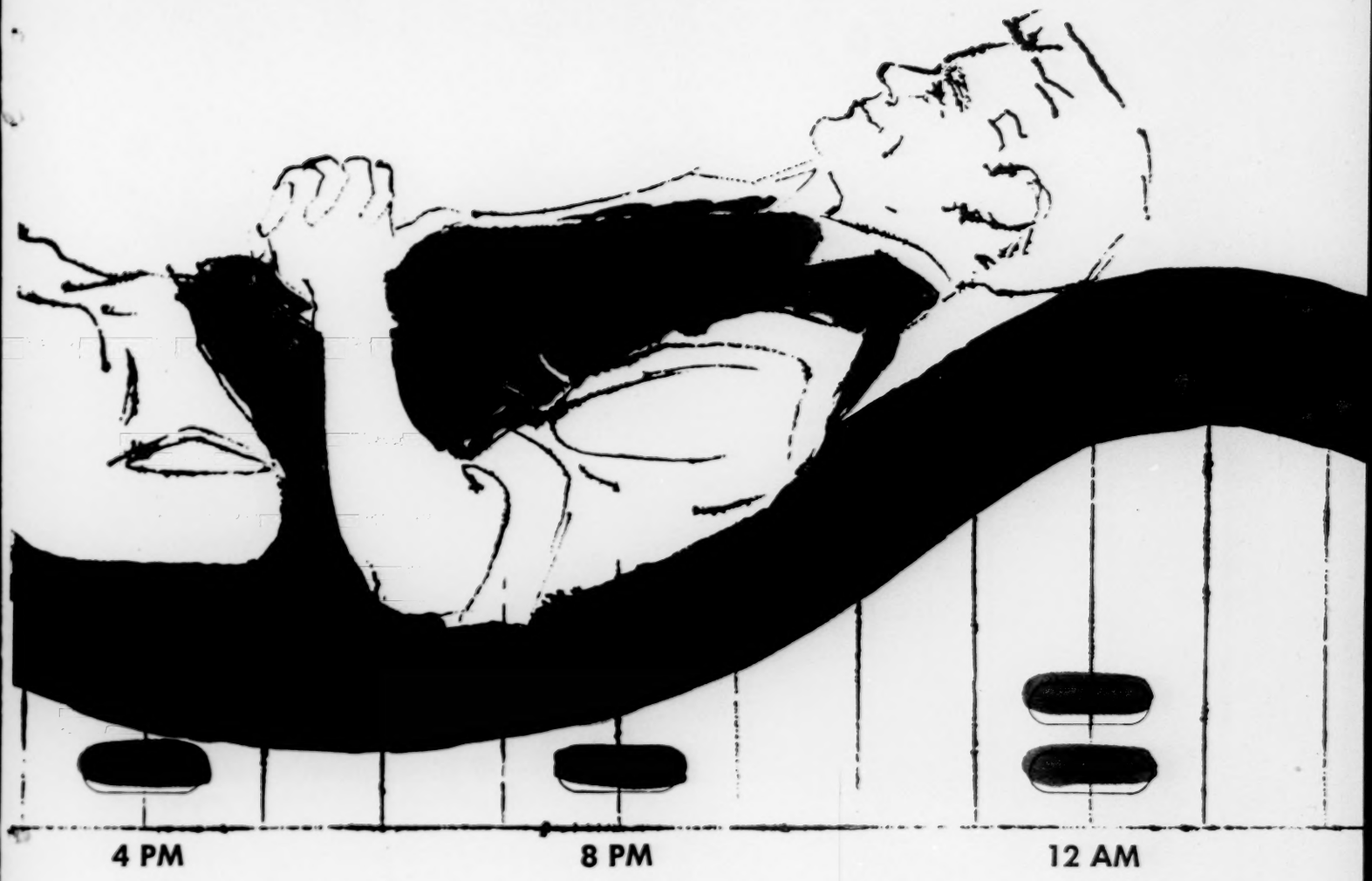
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Coliforms	34	3	*91.8*
Proteus	5	5	*50.0*
A. aerogenes	8	0	*100.0*
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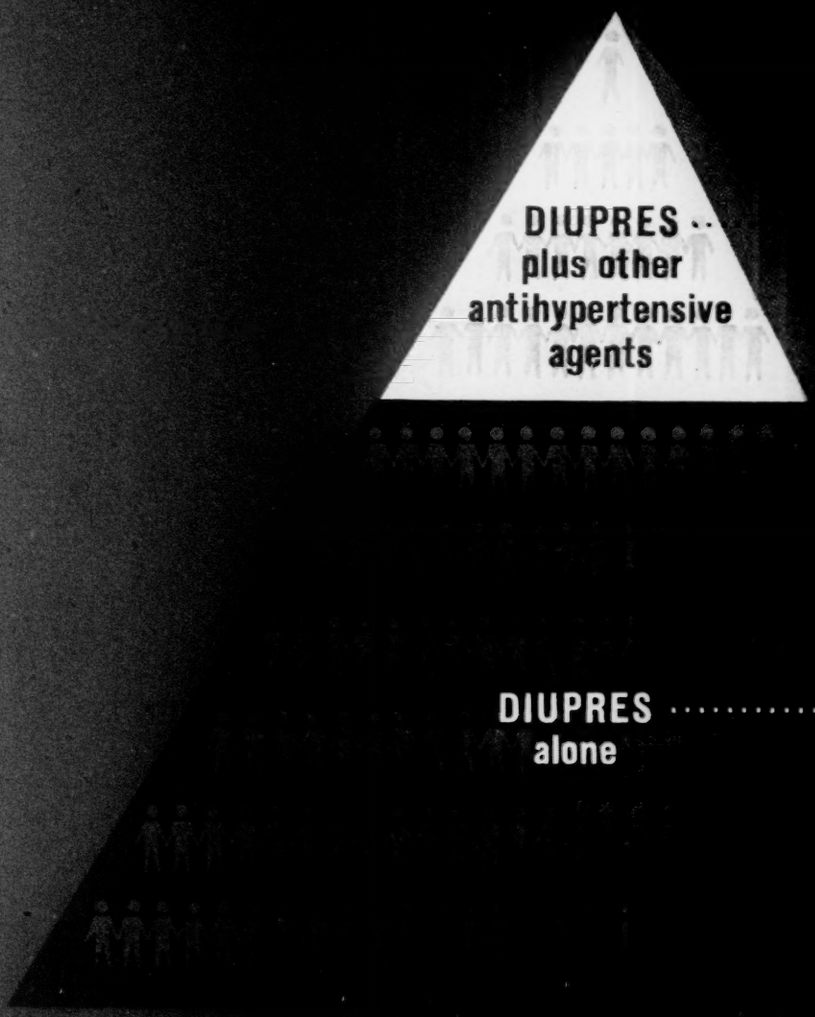
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*Cohen, B. M.: The Ambulatory Patient with Hypertension: An Approach to Office Management, presented at the American Medical Association Convention, San Francisco, California, June 22-27, 1958.

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Date	3/3	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13	3/14	3/15	3/16	3/17	3/18	3/19	3/20	3/21	3/22	3/23
Weight (pounds)	178	176	170	169	167	159	158	158	157	153	155	155	156	154	153	154	153	—	—	151	149
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Miller, R. F.: Clin. Rev. *1*:10 (July) 1958

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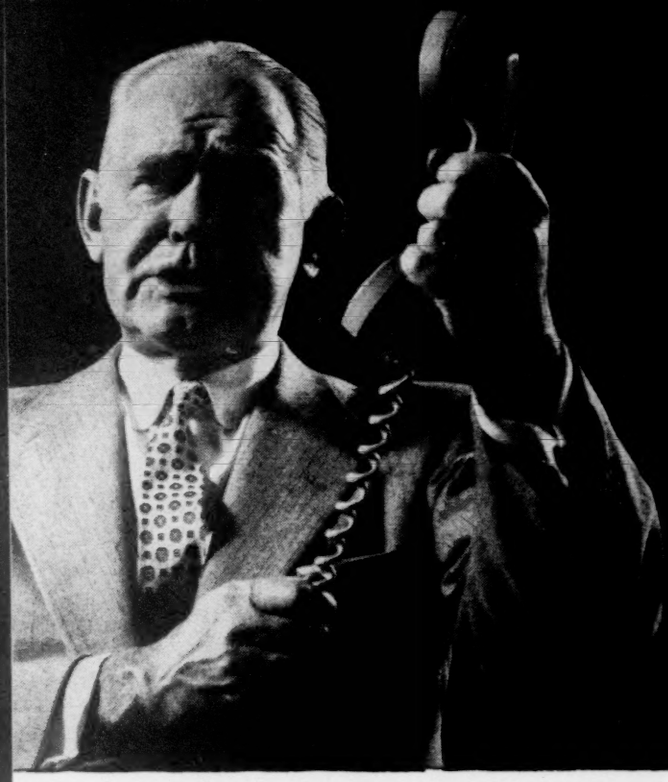
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1. Grossman, A. J.; Batterman, R. C., and Leifer, P.: Fed. Proc. *17*:373 (March) 1958.

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1. Lewis, J.M., et al.: J. Pediatrics, *31*:496

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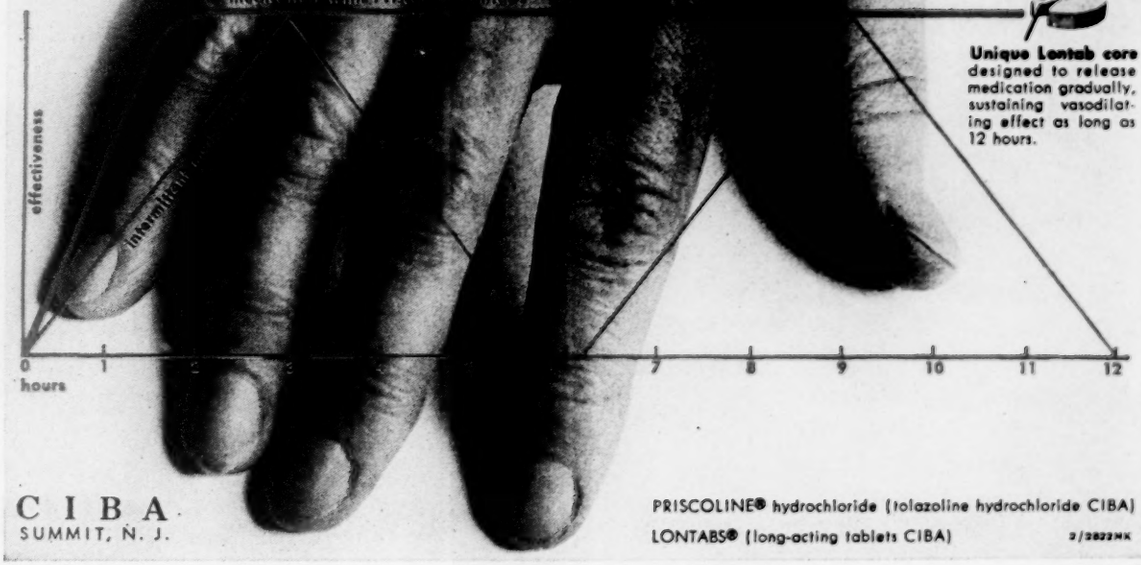
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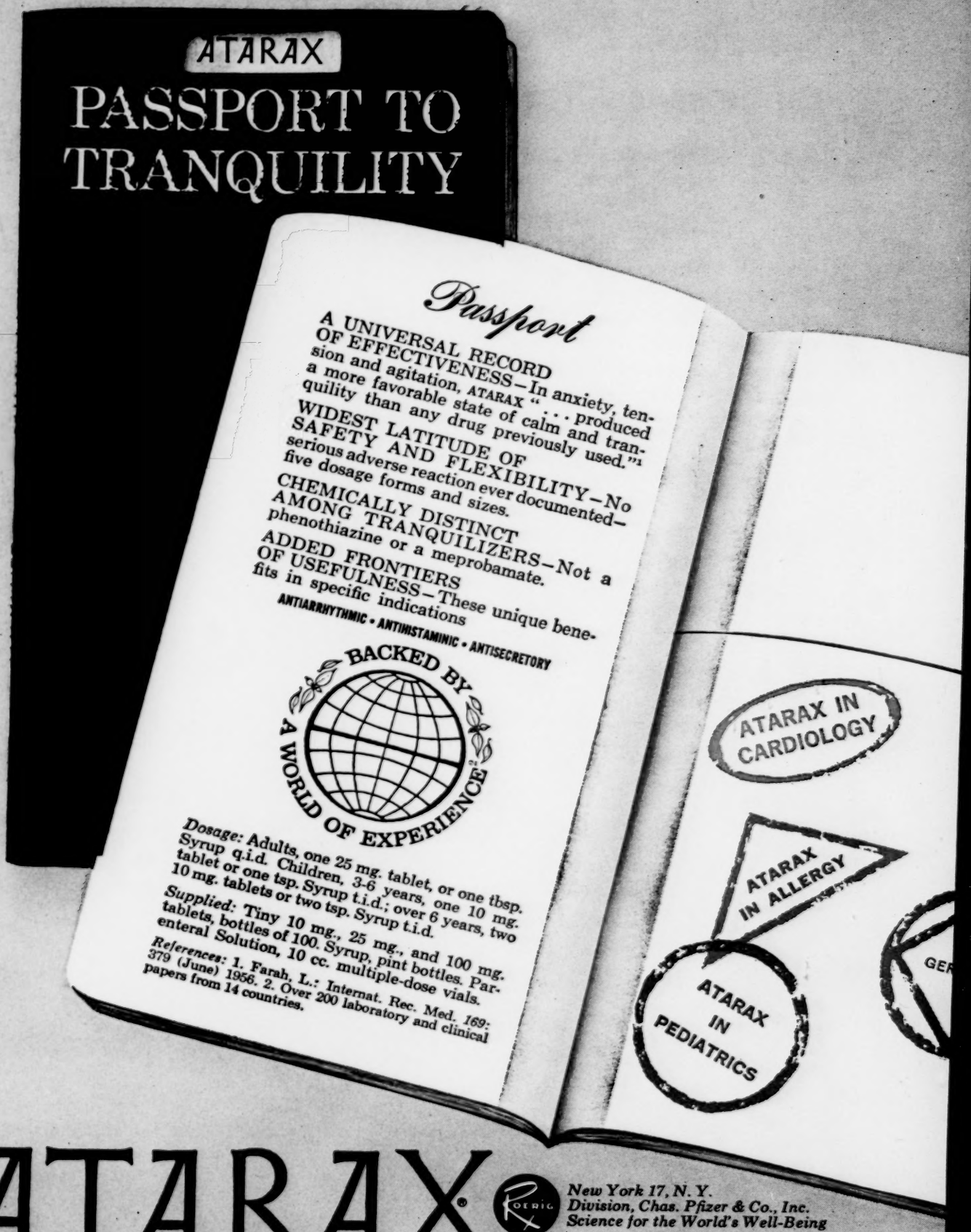
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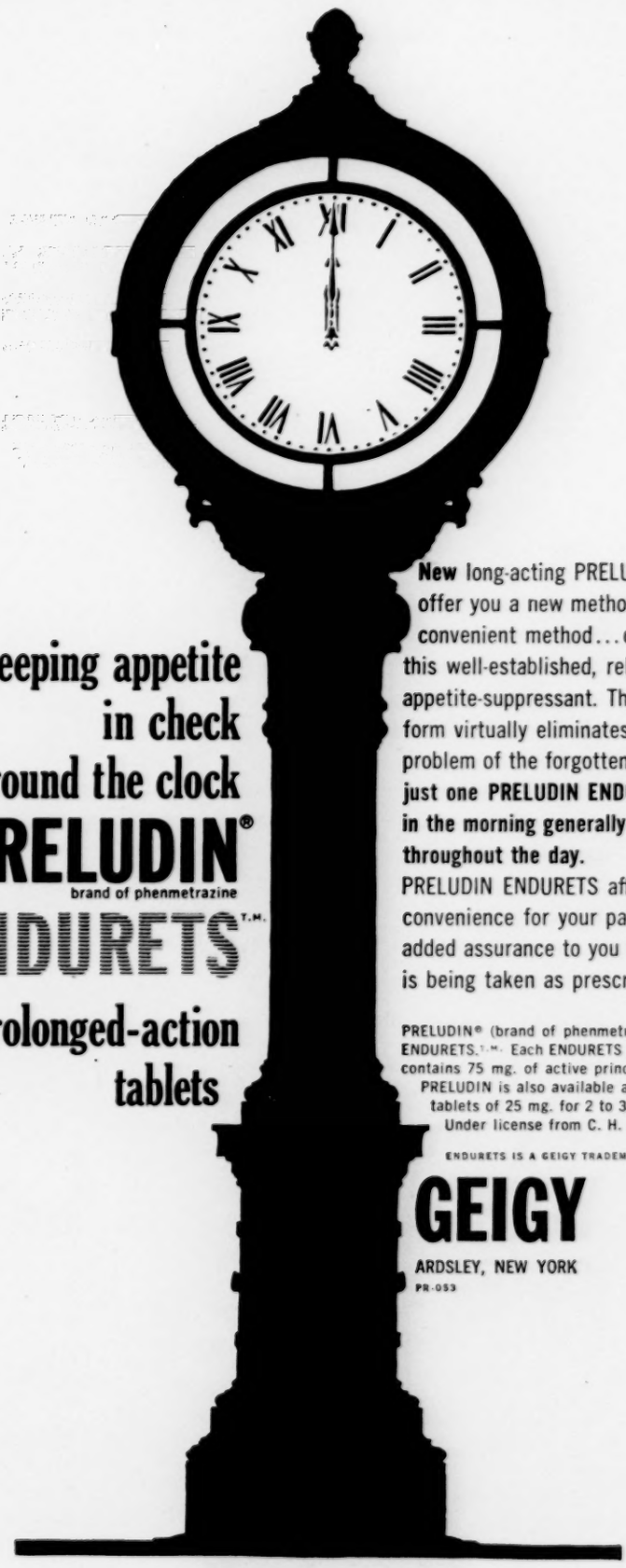
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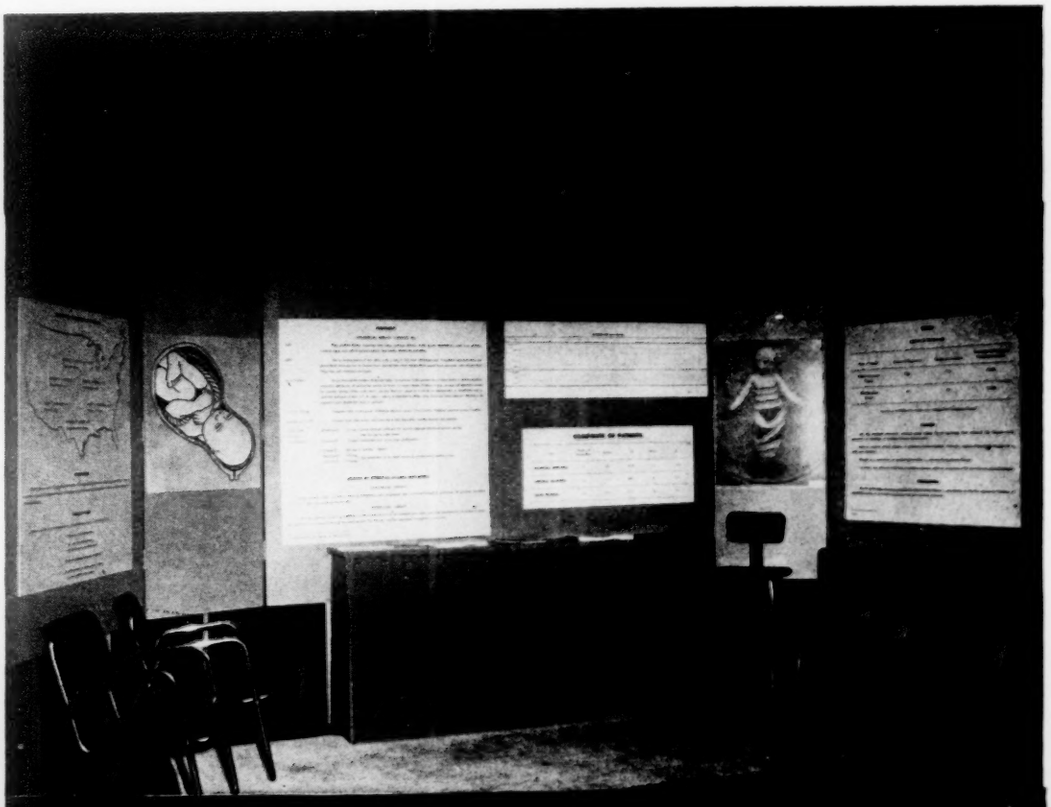
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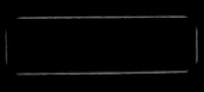
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Supplied: Tablets, scored, pink, bottles of 50.

Dosage: Two tablets three or four times a day.

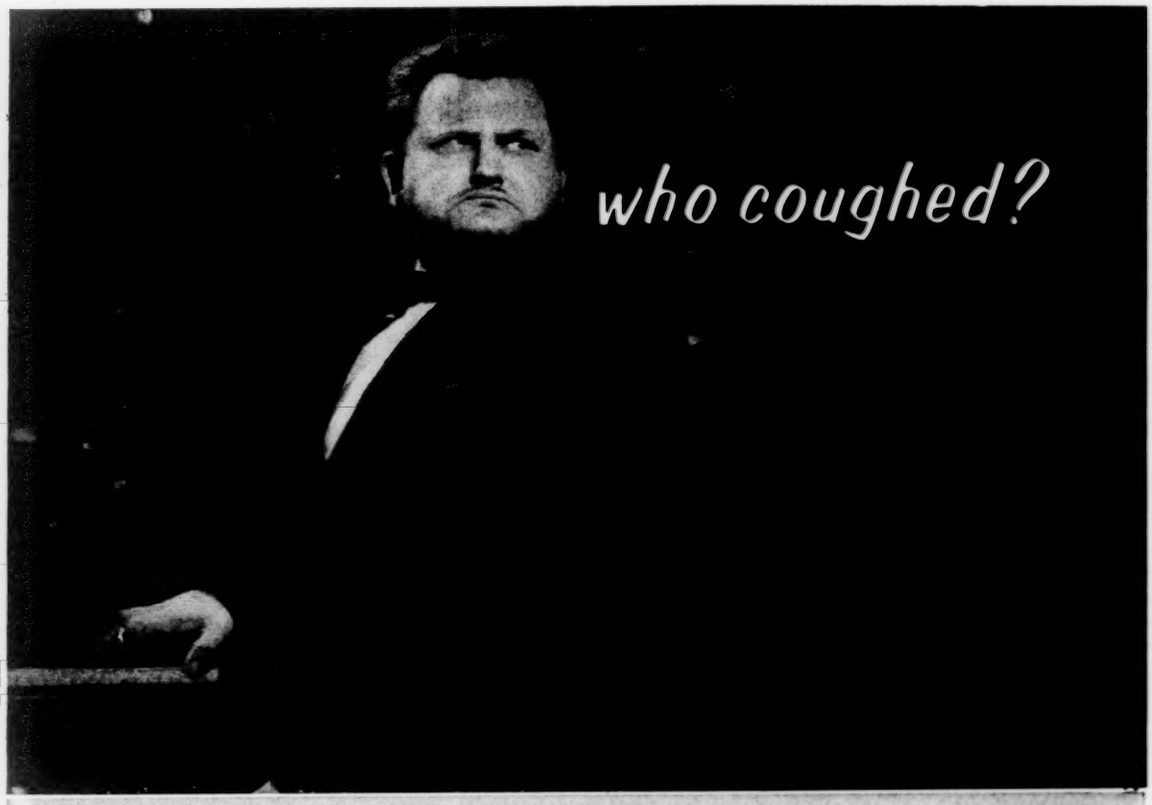
Each PARAFON WITH PREDNISOLONE tablet contains: PARAFLEX® Chlorzoxazone‡ 125 mg., TYLENOL® Acetaminophen 300 mg., and prednisolone 1.0 mg.

Supplied: Tablets, scored, buff colored, bottles of 36.

Dosage: One to two tablets three or four times a day.

Precautions: The precautions and contraindications that apply to all steroids should be kept in mind when prescribing PARAFON WITH PREDNISOLONE.

Trade marks ‡U.S. Patent Pending



WHENEVER COUGH THERAPY IS INDICATED

Hycomine®
SYRUP

THE *complete* Rx FOR COUGH CONTROL

cough sedative / antihistamine / expectorant

- relieves cough and associated symptoms in 15-20 minutes
- effective for 6 hours or longer
- promotes expectoration
- rarely constipates
- agreeably cherry-flavored

Each teaspoonful (5 cc.) of HYCOMINE contains:

Hycodan®		
Dihydrocodeinone Bitartrate (Warning: May be habit-forming)	5 mg.	6.5 mg.
Homatropine Methylbromide	1.5 mg.	
Pyrilamine Maleate		12.5 mg.
Ammonium Chloride		60 mg.
Sodium Citrate		85 mg.

Endo®

Literature on request

Supplied: As a pleasant-to-take syrup. May be habit-forming. Federal law permits oral prescription.

ENDO LABORATORIES Richmond Hill 18, New York

U.S. Pat. 2,630,400

Polanil

POLANIL is dextro-chlorpheniramine maleate (Polaramine® Maleate) — the closest to a perfect antihistamine and dexamethasone (Deronil®) — today's lowest dosage corticosteroid.

What are its advantages?

How is it supplied?

POLARAMINE: the closest to a perfect antihistamine
DERONIL: today's lowest dosage corticosteroid
POLANIL:

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

Schering

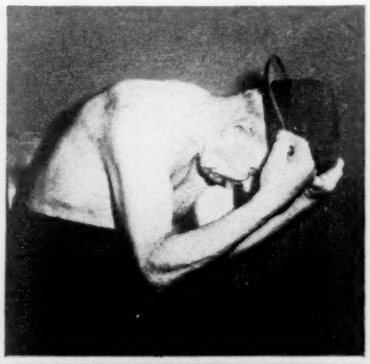
for full corticosteroid benefits: new Gammacorten

this arthritic needed Gammacorten

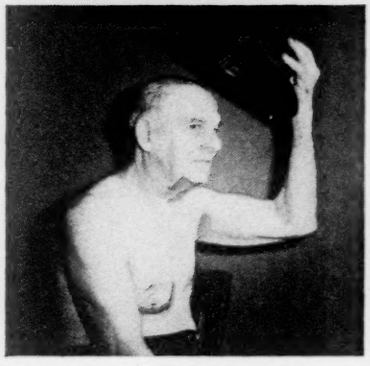
PATIENT M. S., age 81, at time of first visit was in severe pain and very uncomfortable. Complained of swelling of wrists, legs, various joints; there was pain and stiffness in cervical area and lower spine; pain, swelling and limited motion in the fingers; slight ulnar deviation of the hand. He could not raise his arms above the level of his shoulders.

Treatment and Result: After 36 hours of **GAMMACORTEN** therapy, M. S. had "complete relief." Joint swelling had decreased, pain was almost absent, range of motion had increased dramatically. At the end of the first week of **GAMMACORTEN** he was free of discomfort and able to return to his job as a porter.

BEFORE GAMMACORTEN: M. S. demonstrates the position necessary to put on his hat (range of motion was so restricted that he could not comb his hair).



AFTER ONE WEEK OF GAMMACORTEN: **M. S. could put on his hat normally, could comb hair; function near-normal at end of first week of treatment.**



BEFORE GAMMACORTEN: His fingers were extremely painful and were so swollen that a size 11 jeweler's ring would not fit over his small finger.



AFTER ONE WEEK OF GAMMACORTEN: **Size 11 jeweler's ring passes easily over previously swollen joint. At end of first week, "puffiness" had virtually disappeared.**



BEFORE GAMMACORTEN: Hands were so painful, stiff and swollen that M. S. could not flatten hand or extend fingers on flat surface.



AFTER ONE WEEK OF GAMMACORTEN: **Pain completely subsided. M. S. can flatten hand, extend fingers and flex in normal manner without pain.**



Photographs used with permission of patient.

How to use Gammacorten

With **GAMMACORTEN,** a full measure of corticosteroid benefit can now be brought to patients who have heretofore obtained less than optimal benefit from adrenocorticoid therapy. In practice, the increased activity of **GAMMACORTEN** means maximal mobility for the arthritic; maximal freedom from attack for the asthmatic; rapid and complete resolution of lesions for the dermatologic patient. Unwanted adrenocorticoid effects are relatively infrequent with **GAMMACORTEN.** Should side effects occur, they can be usually managed by reducing dosage or by supplemental measures.

in arthritis

— An initial dosage of 1.5 to 3 mg. per day (2 to 4 tablets divided into 3 or 4 doses). This dosage should be continued until a satisfactory symptomatic response is obtained — usually within 3 or 4 days. After a favorable response has been obtained, reduce dosage by 1/3 every 2 to 3 days until either maintenance dosage is established or therapy can be discontinued. Satisfactory control can often be maintained with as little as 0.75 mg. to 1.5 mg. per day.

in asthma and allergy

— **IN STATUS ASTHMATICUS:** Initial daily dosage of GAMMACORTEN is 7.5 to 10 mg. (10 to 13 tablets divided into 3 or 4 doses). As soon as the acute state is controlled, reduce dosage slowly by 1/3 to 1/4 until a satisfactory maintenance level is reached or until therapy is discontinued.

IN CHRONIC BRONCHIAL ASTHMA: Initial dosage is 1.5 to 3 mg. of GAMMACORTEN per day (2 to 4 tablets divided into 3 or 4 doses). After a satisfactory response has been obtained, decrease dosage by 1/3 every 2 to 3 days until either maintenance level has been determined or therapy can be discontinued. Asthmatics can often be maintained for long periods on as little as 0.75 mg. to 1.5 mg. of GAMMACORTEN daily.

IN INTRACTABLE HAY FEVER: Start with 2 to 3 mg. (3 to 4 tablets divided into 3 or 4 doses) of GAMMACORTEN per day. Symptoms should be promptly relieved; prolonged maintenance therapy is unnecessary for these self-limiting disorders.

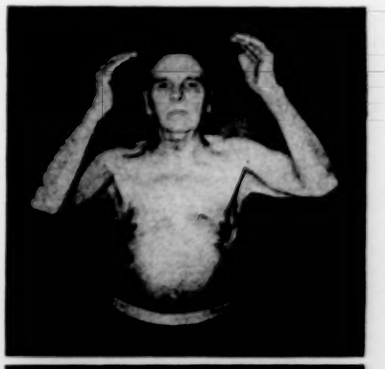
in skin disorders

Start with 2 to 3 mg. (3 to 4 tablets divided into 3 or 4 doses) of GAMMACORTEN daily. Satisfactory control is usually obtained at this dosage level. In chronic conditions, dosage should be decreased by 1/3 every 2 to 3 days until either a satisfactory maintenance level has been achieved or therapy can be discontinued. In acute or self-limiting disorders, treatment may be discontinued as soon as control has been obtained.

SUPPLIED: GAMMACORTEN Tablets, 0.75 mg.

2/2704 MX

BEFORE GAMMACORTEN: **M. S. could not raise arms above shoulder level; even the degree of motion shown was extremely painful.**





AFTER ONE WEEK OF GAMMACORTEN: **Range of motion and rotation dramatically increased; M. S. could move arms without pain for the first time in months.**

Gammacorten T.M.

(dexamethasone CIBA)

...a potent, highly effective corticosteroid; profound anti-inflammatory activity, with minimal potential for corticosteroid side effects

CIBA

IN NAUSEA AND VOMITING OF PREGNANCY



USE

SPECIFIC
Avoids unnecessarily diffuse or diverse drug action; effective in economical once-a-day dosage

ESTABLISHED
6-year record of successful use in daily practice; consistently favorable reports[1-10]

UNCOMPLICATED
Has no known contraindications; free of hepatic, hypotensive, and hematologic hazards observed with phenothiazines

BONAMINE*

brand of meclizine hydrochloride

SUPPLIED:

BONAMINE Tablets, scored, 25 mg.

BONAMINE Chewing Tablets, mint-flavored, 25 mg.

BONAMINE Elixir, cherry-flavored, ideal for children, 12.5 mg. per teaspoonful (5 cc.).

DOSAGE: Adults, 25 to 50 mg. once a day. Children, usually half the adult dose.

BONAMINE REFERENCES:

1. Moyer, J. H.: M. Clin. North America, Mar., 1957, p. 405.
2. Seidner, H. M.: Illinois M. J. 109:20, 1956.
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5. Kinney, J. J.: J. M. Soc. New Jersey 53:125, 1956.
6. Semmens, J. P.: Obst. & Gynec. 9:568, 1957.
7. Conner, P. K., Jr., and Moyer, J. H.: GP 14:124, No. 5, 1956.
8. Danechmar, C. M., et al.: South. M. J. 49:1405, 1956.
9. Mathoris, C. Mc., and Bryans, C. I., Jr.: J. M. A. Georgia 45:46, 1956.
10. Report of study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:756, 1956.

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

Science for the world's well-being™

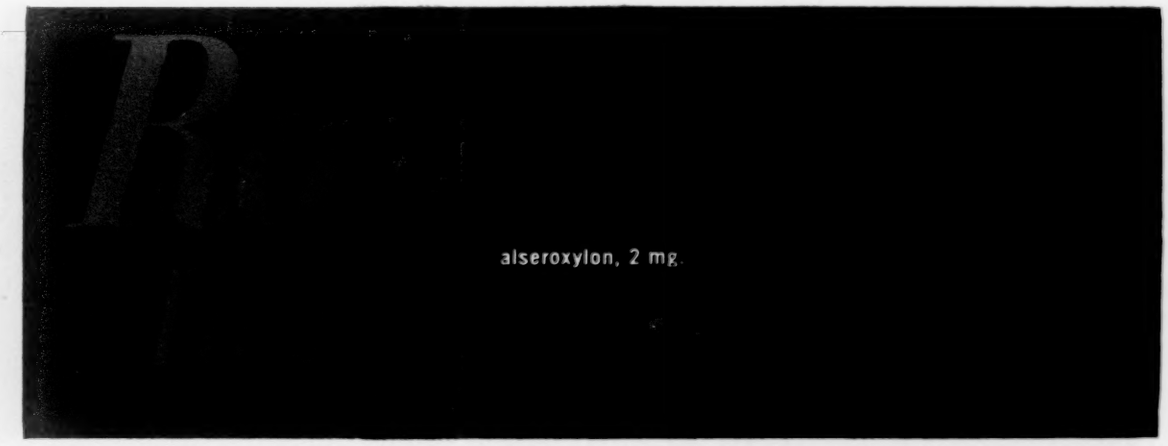
*Trademark

Ideally Suited for Long-Term Therapy*



just two tablets at bedtime

After full effect one tablet suffices



*Because RAUWILOID provides effective Rauwolfia action virtually free from serious side effects... the smooth therapeutic efficacy of Rauwiloid is associated with a lower incidence of certain unwanted side effects than is reserpine... and with a lower incidence of depression. Tolerance does not develop.

RAUWILOID can be initial therapy for most hypertensive patients... Dosage adjustment is rarely a problem.

When more potent drugs are needed, prescribe one of the *convenient single-tablet combinations*

Rauwiloid® + Veriloid®
alseroxylon 1 mg. and alkavervir 3 mg.

or

Rauwiloid® + Hexamethonium
alseroxylon 1 mg. and hexamethonium chloride dihydrate 250 mg.

Many patients with severe hypertension can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.

Riker
Northridge, California

whichever you choose



you provide vitamin protection to help maintain health and energy during the early years of rapid growth.

APPLE-FLAVORED

ABDEC® DROPS

comprehensive multivitamin formula

Each 0.6 cc. supplies:

Vitamin A	5,000 units
Vitamin D	1,000 units
Vitamin C (ascorbic acid)	50 mg.
Vitamin B_1 (thiamine hydrochloride)	1 mg.
Vitamin B_2 (riboflavin)	1.2 mg.
Vitamin B_6 (pyridoxine hydrochloride)	1 mg.
Pantothenic acid (as the sodium salt)	5 mg.
Nicotinamide (niacinamide)	10 mg.

In bottles of 15 and 50 cc. with calibrated plastic droppers.

ORANGE-LIME FLAVORED

ADC DROPS

with Vitamin B_6

Each 0.6 cc. supplies:

Vitamin A	5,000 units
Vitamin D	1,000 units
Vitamin C (ascorbic acid)	50 mg.
Vitamin B_6 (pyridoxine hydrochloride)	1 mg.

ADC Drops with Vitamin B_6 in bottles of 15 and 50 cc. with calibrated plastic droppers.

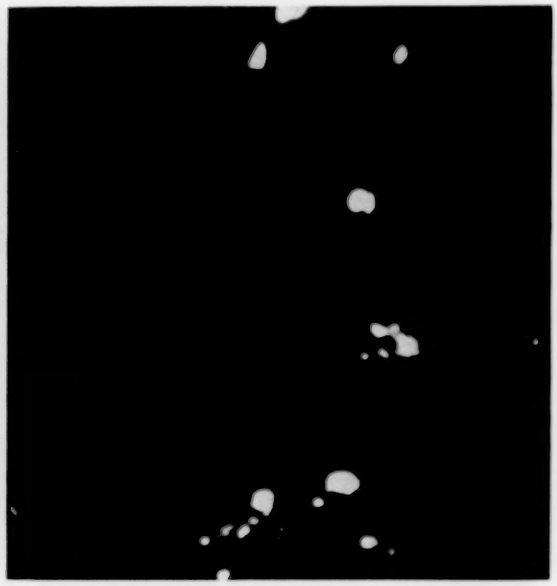
PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN 94459

MEDICAMENTA PERA

Clarin* can do this for your postcoronary patients



WITHOUT CLARIN, turbid blood serum five hours after a fat meal: This unretouched dark-field photomicrograph (2500X) shows potentially hazardous fat concentrations circulating in the blood stream of a patient after a standard fat meal.



WITH CLARIN, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

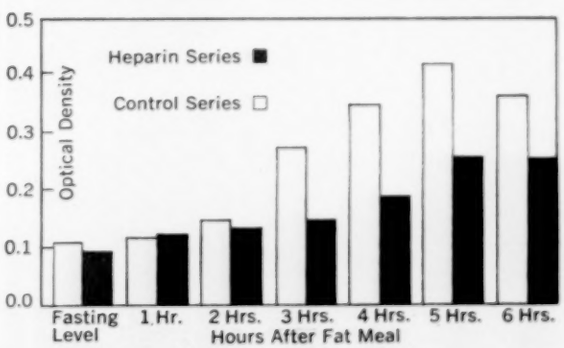
CLARIN is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of postprandial lipemic serum."[1] Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.[1] It therefore provides important benefits for your postcoronary patients.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.



Average serum optical density in 36 patients after fat meal with and without sublingual heparin.[2]

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc. New York 17, N. Y.

Why Claysorb means more effective antidiarrheal treatment

The response to an antidiarrheal preparation is directly linked to the effectiveness of its adsorbent. In both POLYMAGMA and POLYMAGMA Plain, the new agent Claysorb* gives you a previously unattainable adsorptive power . . . proved to be five times beyond that of kaolin in removing diarrhea-causing toxins. In addition, POLYMAGMA and POLYMAGMA Plain protect the irritated intestinal walls, promote well-formed stools, help restore healthy intestinal function.

POLYMAGMA
For bacterial diarrhea—
bactericidal against many pathogens

POLYMAGMA Plain
For nonbacterial diarrhea—
same formula but without antibiotics

Polymagma®

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb* (Activated Attapulgite, Wyeth) in Alumina Gel

*Trademark

Wyeth
Philadelphia 1, Pa.



INTRODUCING

RUBRAMIN PC

SQUIBB VITAMIN B_{12} U.S.P. INJECTION

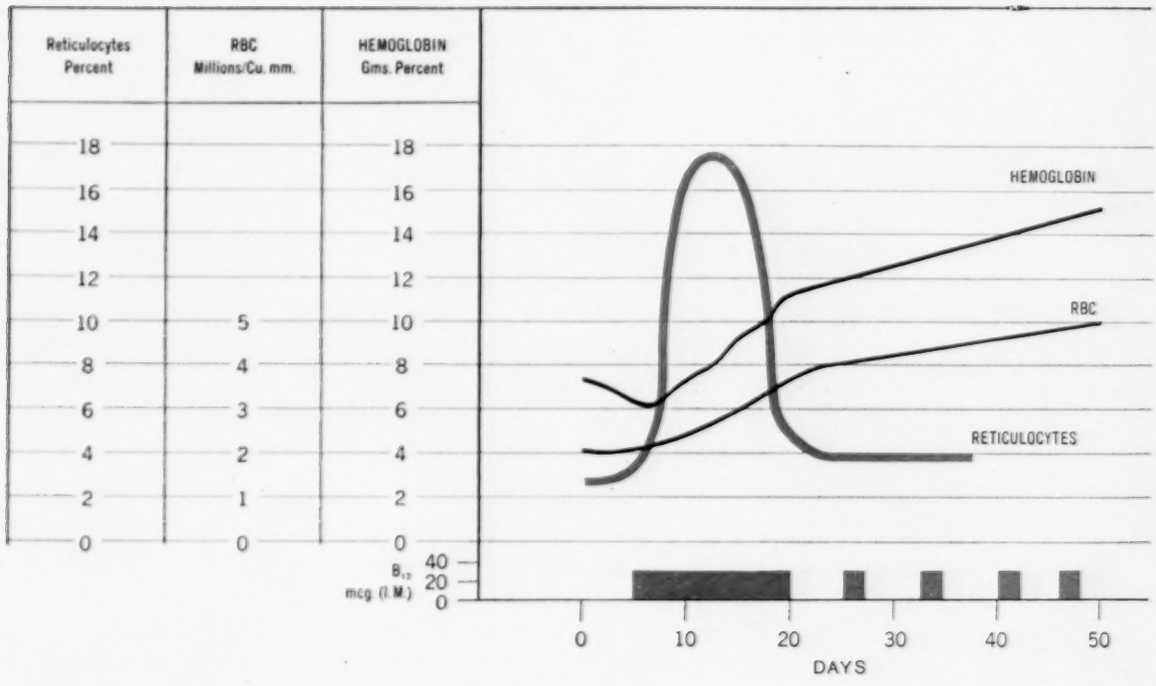
PURE CYANOCOBALAMIN INJECTION – CREATED AND PRODUCED BY SQUIBB – FOR THE MOST EXACTING STANDARDS OF INTRAVENOUS, INTRAMUSCULAR AND SUBCUTANEOUS ADMINISTRATION IN:

- *pernicious anemia*
- *severe nutritional macrocytic anemias*
- *severe nutritional neuropathies*
- *prevention of macrocytic anemia following partial or total gastrectomy*

and for the relief of pain in such conditions as:

trigeminal neuralgia; osteoarthritis; secondary burning paresthesias; herpes zoster; and neuroblastoma in children.

RUBRAMIN PC is highly effective whenever high doses of vitamin B_{12} are required.



TYPICAL HEMATOPOIETIC RESPONSE WHEN RUBRAMIN P C IS GIVEN INTRAMUSCULARLY TO A PATIENT WITH MEGALOBLASTIC ANEMIA *(schematic)*

highly potent and vital to metabolism

Vitamin B_{12} – one of the most potent biological factors known – is vital to basic metabolic functions, to normal formation of red blood cells and other formed elements of the blood, and to the functional integrity of myelinated fibers in the spinal cord and brain, as well as to the healthy condition of gastric and oral mucosa.

therapeutic agent of choice in pernicious anemia

Vitamin B_{12} is the therapeutic agent of choice in pernicious anemia, is effective in certain megaloblastic macrocytic anemias, and contributes to recovery or clinical improvement in a variety of neurological, liver and skin disorders.

non-toxic, remarkably free from side reactions

Despite its high level of activity, vitamin B_{12} is non-toxic and remarkably free from side reactions. It has been well-tolerated even when administered in massive doses.

potency confirmed by precise radioisotope measurement

The Radioisotope Tracer Method is now used routinely as an assay procedure in the production of RUBRAMIN, guaranteeing accurate label potency.

RUBRAMIN P C is now available in potencies for all your parenteral requirements: 30, 50 and 100 mcg. per cc., 10 cc. vials; 1000 mcg. per cc., 1 cc. and 10 cc. vials.

SQUIBB *Squibb Quality—the Priceless Ingredient*

"RUBRAMIN"® IS A SQUIBB TRADEMARK

new for total management of itching,[1,2] inflamed,[3,4] infected[5,6] skin lesions



Dermatitis repens with staph and monilia 7 weeks duration

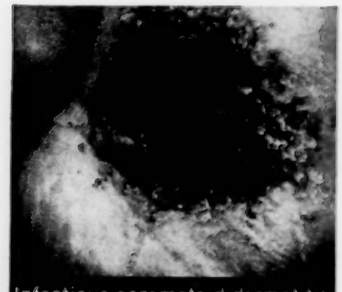


Cleared in 5 days

Mycolog ointment

Kenalog, Spectrocin and Mycostatin in Plastibase

antipruritic/anti-inflammatory/antibacterial/antifungal



Infectious eczematoid dermatitis of ankle 5 years duration



Cleared in 20 days

Mycolog Ointment – containing the new superior topical corticoid Kenalog – reduces inflammation,[3,4] relieves itching,[1,2] and combats or prevents bacterial, monilial and mixed infections.[5-7] It is extremely well tolerated, and assures a rapid, decisive clinical response for most infected dermatoses.

> "Thirty-one of 38 patients . . . obtained excellent or good control of dermatological lesions . . . [Mycolog] was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2 to 3 weeks."[5]

For total management of itching, inflamed, infected skin lesions, Mycolog contains triamcinolone acetonide, an outstanding new topical corticoid for prompt, effective relief of itching, burning and inflammation[1-4] – neomycin and gramicidin for powerful antibacterial action[7] – and nystatin for treating or preventing Candida (Monilia) albicans infections.[8,9]

Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in PLASTIBASE.

References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.; Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

And whatever the topical corticoid need, a suitable Squibb formulation is available—Kenalog-S Lotion—7½ cc. plastic squeeze bottles. Each cc. supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base and 0.25 mg. gramicidin. Kenalog Cream, 0.1%—5 Gm. and 15 Gm. tubes. Kenalog Lotion, 0.1%—15 cc. plastic squeeze bottles. Kenalog Ointment, 0.1%—5 Gm. and 15 Gm. tubes.

SQUIBB

Squibb Quality — the Priceless Ingredient

"SPECTROCIN"®, "MYCOSTATIN"®, "PLASTIBASE"®, "MYCOLOG" AND "KENALOG" ARE SQUIBB TRADEMARKS



AN ELECTROCARDIOGRAPH for maximum usefulness in your *office examining room* . . . and an electrocardiograph that you can easily *take with you* on any call — are the reasons Sanborn Company developed the 100 Viso and 300 Visette ECG's.

Both produce permanent, easily interpreted, diagnostically accurate electrocardiograms. Both are simple to operate . . . and both will give stable, trouble-free operation year after year. But there are also these important differences: in the 18-pound Visette, every *practical* means is used to achieve the combination of extremely light weight, brief case size and "traveling" ruggedness. In the new 100 Viso for office use, where instrument portability is not a prime requirement, the design includes such additional features as *two* recording speeds, *three* recording sensitivities, provision for recording *other* waveforms, and *visual monitoring* by an external oscilloscope.

Each of these companion 'cardiographs has individual emphasis in terms of *portability* and *versatility*. But both equally reflect the best principles of modern diagnostic instrument design.

SANBORN COMPANY
MEDICAL DIVISION
175 WYMAN ST., WALTHAM 54, MASS.

Model 300 Visette, 625 dollars.
Model 100 Viso, 850 dollars.
Delivered prices, continental U. S. A.

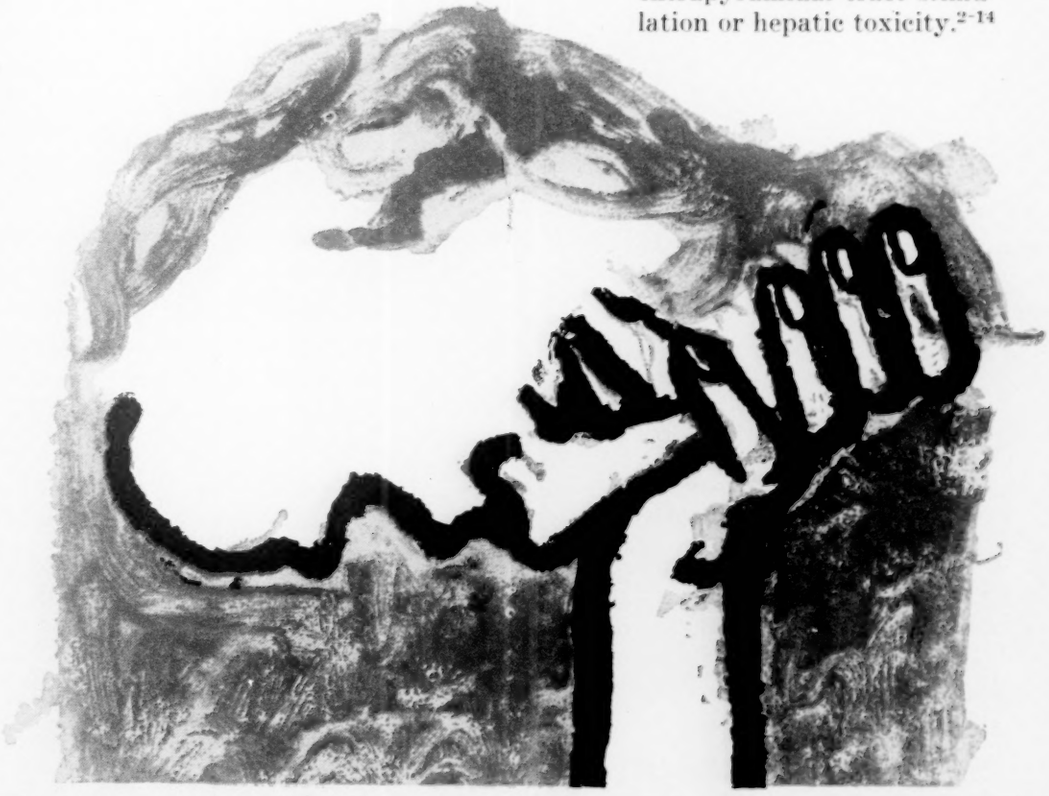
stop as well as prevent nausea and vomiting

NEW Tigan

now in oral, parenteral, and suppository forms

effective but not "side effective"

Tigan blocks emetic impulses at the chemoreceptor trigger zone (CTZ),[1] a medullary structure activating the vomiting center. While Tigan shares with the phenothiazines the mode of antiemetic action, this is their only similarity.[1] In extensive clinical studies[2-14] Tigan, unsurpassed in specificity, has exhibited a virtually complete absence of side effects. Tigan has demonstrated no sedative or tranquilizing properties, no hypotensive or supramedullary effects, no extrapyramidal tract stimulation or hepatic toxicity.[2-14]



no special precautions—
no known contraindications

in nausea/vomiting of gastrointestinal disorders — Complete or moderate relief in 78 per cent of acute or chronic gastroenteritis patients;[13] "We did not find a single toxic reaction . . . no side effects, such as sedation, skin rash . . . no changes in pulse, respiration, or . . . blood pressure."[13]

in nausea/vomiting of pregnancy — No evidence of sedation or other side effects[12] observed in a series of patients of whom 94 per cent became asymptomatic on Tigan. On other antiemetic medication, several had failed to respond or had complained of drowsiness.[12]

in nausea/vomiting of radiation sickness — Protected with Tigan ". . . not one patient had to discontinue [deep radiation] treatments. . . ."[5]

in nausea/vomiting of drug administration — ". . . large intermittent dose[s] of [nitrogen mustard and other drug] therapy could be given without the associated nausea and vomiting that we had seen before."[7]

Tigan

specific antiemetic antinauseant

no sedative properties
no tranquilizer side effects

Suggested uses: Both prophylactic and therapeutic control of nausea and vomiting associated with pregnancy, travel sickness, gastrointestinal disorders, operative procedures, carcinomatoses, toxicoses, other underlying disease processes, drug administration and radiation therapy.

Dosage: Adults — 1 or 2 capsules, orally, 2 cc intramuscularly, q.i.d. or 1 suppository, q.i.d. For children's dosage, consult literature.

In nausea and vomiting of pregnancy — Satisfactory control is usually achieved with an initial dose of two capsules immediately upon awakening. If possible, the patient should remain in bed for one-half to one hour following this dose. When nausea and vomiting are not confined to the morning hours, supplemental doses of one or two capsules should be given throughout the day at intervals of three to four hours.

How Supplied: Tigan capsules, 100 mg, blue and white — bottles of 100 and 500. Tigan ampuls, 2 cc (100 mg/cc)— boxes of 6 and 25. Tigan Pediatric Suppositories, 200 mg, boxes of 6 and 25.

TIGAN®: Hydrochloride-4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl)-benzylamine hydrochloride ROCHE®

References: **1.** W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, in press. **2.** W. B. Abrams, I. Roseff, J. Kaufman, L. Goldman and A. Bernstein, to be published. **3.** I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.*, 9:189, 1958. **4.** O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. **5.** J. A. Lucinian, *ibid.* **6.** D. W. Molander, *ibid.* **7.** B. I. Shnider, *ibid.* **8.** W. S. Derrick, *ibid.* **9.** B. Wolfson and F. F. Foldes, *ibid.* **10.** L. McLaughlin, *ibid.* **11.** Reports on file, Roche Laboratories. **12.** Personal communications. **13.** W. K. Gauthier, Discussant at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. **14.** H. E. Davis, *ibid.*

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley 10, N. J.



DARVON® COMPOUND potent · safe · well tolerated

The clinical usefulness of Darvon® (dextro propoxyphene hydrochloride, Lilly), alone and in combination, has been substantiated by more than 100 investigators in the treatment of over 6,300 patients in pain. A consolidation of these reports shows that 5,663 (89.8 percent) experienced "effective analgesia."

Darvon Compound combines in a single Pulvule® the analgesic action of Darvon with the antipyretic and anti-inflammatory benefits of A.S.A.® Compound (acetylsalicylic acid and acetophenetidin compound, Lilly). When inflammation is present, Darvon Compound reduces discomfort to a greater extent than does either analgesic given alone.

Usual dosage: 1 or 2 Pulvules three or four times daily.

Also available: Darvon, in 32 and 65-mg. Pulvules.

Usual dosage: 32 mg. (approximately 1/2 grain) every four hours or 65 mg. (1 grain) every six hours.

Darvon® Compound (dextro propoxyphene and acetylsalicylic acid compound, Lilly)

ELI LILLY AND COMPANY · INDIANAPOLIS 6, INDIANA, U.S.A.

920749

The American Journal of Medicine

VOL. XXVII SEPTEMBER, 1959 NO. 3

Editorial

Computers and Experimental Medicine

BECAUSE of their ability to perform a wide range of complex computations at a high rate of speed, electronic computers can be powerful tools for studying the complex systems found in the biological sciences. Technical and industrial advances in the past few years have made available computers which can fit the technical and financial capabilities of almost any laboratory. For these reasons, it is worthwhile to consider the place of computers in the experimental study of biological systems, the types of instruments available, and the manner in which some of them are used.

The strengths and weaknesses of computers as experimental aids are best considered in relationship to the general methodology of experimentation. The experimental study of any system involves collection of data, formulation of hypotheses to explain the data, and examination of these hypotheses to find areas which may be tested experimentally. Hypotheses are usually examined by using them to predict the behavior of specific parts of the system. These predictions can then be tested experimentally and the hypothesis modified to fit the new experimental findings. It is often difficult to make such predictions from hypotheses which concern biological systems, because of the complexity of the operations performed by individual units of the system (e.g., nephrons, alveoli, etc.), the large number of units involved, and the complexity of the interrelationships between units. Since they can perform numerous, interrelated, complex operations very rapidly, computers can often make such predictions quickly enough to be practical. Herein lie both the strengths and the limitations of the computer. It may increase the productiveness of a hypothesis by increasing its yield of experiments and may help to choose experiments best suited to the methods at hand. In doing so, however, it is entirely dependent upon the quality of the hypothesis and the quality of the data used in making the prediction. It is not a substitute for the creative imagination of the investigator or for careful collection of data.

Computers available for such purposes fall into two broad categories, analogue and digital. They differ from each other in principle of operation, accuracy, complexity and cost. Analogue computers accept and manipulate quantities as physical counterparts (length, voltage, and the like), a simple form being the slide rule. The accuracy of any single operation performed by an analogue computer rarely exceeds 0.1 per cent and the over-all accuracy of a long series of operations may be much less. However, these computers are relatively simple and inexpensive and can be purchased and operated much as any other laboratory instrument.

Digital computers accept and manipulate quantities as numbers, a simple form being the desk adding machine. The accuracy of single operations and of series of operations is much greater than that of analogue computers; and the great flexibility of these computers permits them to handle problems which analogue computers cannot. They are, however, very expensive to purchase or rent, and require of the operator a high order of mathematical and technical capability.

Since analogue computers fall within the

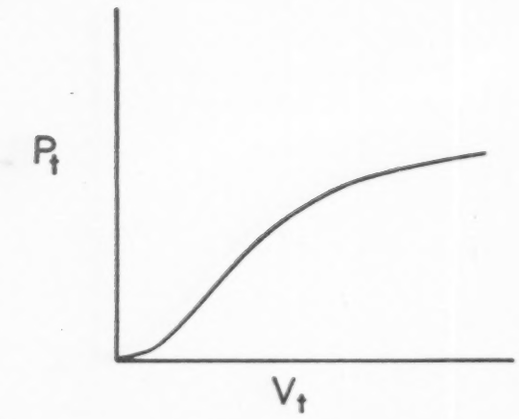


FIG. 1. Relationship between volume of the compartment (V_t) and the pressure difference across its wall (P_t).

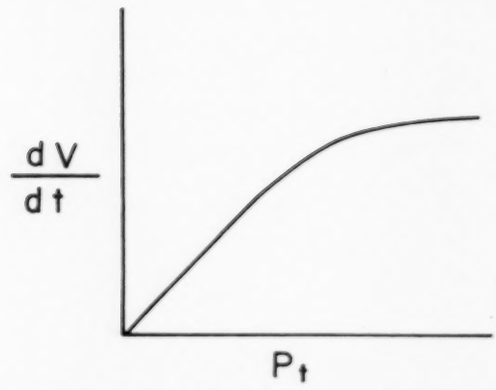


FIG. 2. Relationship between pressure-difference across the channel of exit (P_t) and volume flow through it (dV/dt).

range of financial and technical capability of most laboratories, we will consider their characteristics and mode of operation in some detail.

Analogue computers of the types which are now readily available perform operations on voltages. A voltage is made numerically equal to a variable in the problem (e.g., 1 volt = 5 ml./minute oxygen uptake) and the components in a portion of the computer are so arranged that the desired operation (e.g., subtraction, integration) is performed on the voltage.

The computer can be made to perform a number of operations, among them the following: (1) addition and subtraction, (2) multiplication or division by a constant, (3) integration, (4) multiplication or division of two variable quantities, (5) non-linear functional transformation. This last operation can be performed if a graph of the function is available even though the equation is not known. For example, if one component of the computer is arranged to represent the oxyhemoglobin dissociation curve and a voltage proportional to the partial pressure of oxygen is fed into it, its output is a voltage proportional to oxygen content.

Programming the computer to solve a problem simply amounts to deciding which operations must be performed in which sequence. The procedure is quite simple although it may appear a bit difficult because of its unfamiliarity. It is best illustrated by devising a program to solve a relatively simple problem which would be quite laborious to solve without the computer.

Consider the case of an elastic compartment whose pressure-volume diagram is non-linear and which is emptied through a channel in which the relationship between driving force and flow is non-linear. This system might represent a lung, a vascular compartment, or any one of a number of other components of a biological system. The first step is to identify the variables in the problem and to describe them in terms of constants and other variables. In this problem the variables are the pressure-difference between the inside and outside of the compartment at any time (P_t), the volume of material in the compartment at any time (V_t), and the rate at which material leaves the compartment (dV/dt). The relationship between the volume of the compartment (V_t) and the pressure difference across its wall (P_t) (which may have been established experimentally) can be expressed graphically as shown in Figure 1. The relation between flow through the channel of exit (dV/dt) and the driving force (P_t) (which may also have been determined experimentally) can also be expressed graphically. (Fig. 2.) Furthermore, the volume in the compartment after any interval of time equals the volume in the compartment at the beginning minus the quantity which has left in the interval. These relationships may be restated in symbols in the following equations:

$$P_t = f(V_t) \quad (1)$$

$$dV/dt = \phi(P_t) \quad (2)$$

$$V_t = V_0 - \int_0^t (dV/dt)\, dt \quad (3)$$

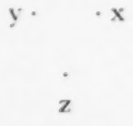
where V_0 = the volume in the compartment at the start of the experiment

$f(\ )$ = the relationship between volume and pressure shown in Figure 1

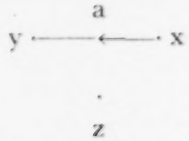
$\phi(\ )$ = the relationship between driving force and flow described in Figure 2.

Several methods are available for converting this set of equations to a wiring diagram for the computer. One of the most easily and generally applicable of these methods is the signal-flow diagram [*1,2*]. Such a diagram is constructed by representing variables as points and operations on variables as lines with arrows. For example, the equation $y = ax - bz$ is diagrammed as follows:

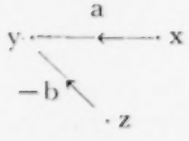
Three points, one for each variable, are placed in any convenient arrangement



A line drawn to indicate the fact that y comes from x through the operation a



A second line is drawn to indicate the fact that y also comes from z through the operation $-b$.



By following this scheme, equations 1, 2 and 3 lead to the diagram shown in Figure 3. This diagram can now serve as the guide for wiring the computer. Each point in the diagram represents a terminal in the computer. Each line in the diagram is a connection through a set of components which perform the operation written beside the line. The components are chosen in accordance with the instructions in the manual furnished with the computer. Solutions may be read out, on any of the recorders commonly used in the laboratory, as graphs of any of the variables (V_t, P_t, dV/dt) with respect to time.

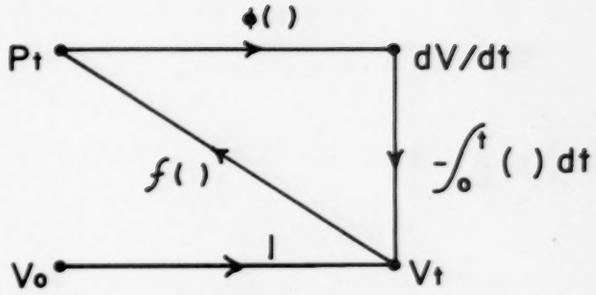


FIG. 3. Signal-flow diagram representing equations 1, 2, and 3 in text.

Several things should be noted about the programming procedure: (1) Little knowledge of electronics is required to solve the problem. Certain combinations of components perform certain operations. The operator need not know why. (2) Virtually no knowledge of operational mathematics is required. The equations are simple descriptions of relationships and are not subjected to any manipulation. For example, the operator need not know how to integrate an expression, only that the expression requires integration. (3) The intellectual labor lies where it belongs, in writing the equations and in interpreting the solutions. The steps between are purely mechanical and governed by a strict but easily applicable set of rules (those governing construction of the signal-flow diagram and those in the instruction manual of the computer).

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[1] MASON, S. J. Feedback theory: some properties of signal-flow graphs. *Proc. I.R.E.*, 41: 1144–1156, 1953.

[2] MASON, S. J. Feedback theory: further properties of signal-flow graphs. *Proc. I.R.E.*, 44: 920–926, 1956.

Clinical Studies

A General Theory of the Causes of Murmurs in the Cardiovascular System*

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MOST physicians accept without question the entrenched theory that cardiovascular murmurs are the result of turbulence in flowing blood. In the present paper evidence will be given to show that this theory lacks validity. In its place a new theory will be proposed.

THE TURBULENCE THEORY OF MURMURS

There is at least a sound physical basis for the belief that murmurs are due to turbulence. Many years ago Reynolds [*1*] demonstrated that when fluid† flow was described in terms of viscosity, velocity and tube diameter, a ratio could be written which would be indicative of the development of turbulence. Thus,

$$R = \frac{(\text{diameter})(\text{velocity})}{\text{viscosity}}$$

where R is termed the Reynolds number. If this exceeds a critical value (2,000), flow which was previously laminar will be found to be turbulent. Because the physical values of blood being propelled through stenotic valves were of such magnitude as to exceed the critical Reynolds number it was believed that murmurs were due to turbulence in flowing blood.

This theory was found to be applicable to conditions without stenosis but in which murmurs were found, and this constituted a strong argument for its widespread acceptance. It readily served as an explanation for the very frequent association of murmurs with anemias. In these conditions the viscosity of blood decreases, and no increase in velocity, such as occurs when blood passes through a region of narrowing, was required before a critical Reynolds number was exceeded. Again, in high output states, which it is now known include anemias, the increased velocity would lead one to expect turbulence. Thus the absence of a stenotic valve did not invalidate the theory. (Fig. 1.)

The Concept of Turbulence. The concept that turbulence in blood would lead to the production of murmurs nevertheless is not likely to be valid. Any region of turbulence can be considered to be composed of fluid which moves randomly both in direction and in velocity. It is statistically inherent in such motion that few forces exist at any instant which dominate any and all others. For sound to be radiated beyond the region of turbulence, however, it is necessary that there be some forces which may be utilized as accoustical energy. This may be roughly expressed by stating that so much energy is consumed by turbulent motion itself that very little remains for interaction with non-turbulent regions. This does not deny the existence of large energy gradients in the forward motion and over-all pressure of a column of moving blood. These, however, occur approximately once each second with each heart beat and cannot thus be considered as a source of sound, for it is well known that sound frequencies less than 20 c.p.s. are inaudible. The concept, therefore, that the presence of turbulence in blood is likely to produce murmurs *assumes* that there is a direct relationship between turbulence and

† At the outset it should be noted that the term "fluid" includes both gases and liquids. The vast majority of articles from the physical literature referred to hereinafter have been written with gas flows in mind. However, the findings are applicable to liquid flows by a simple substitution of appropriate values.

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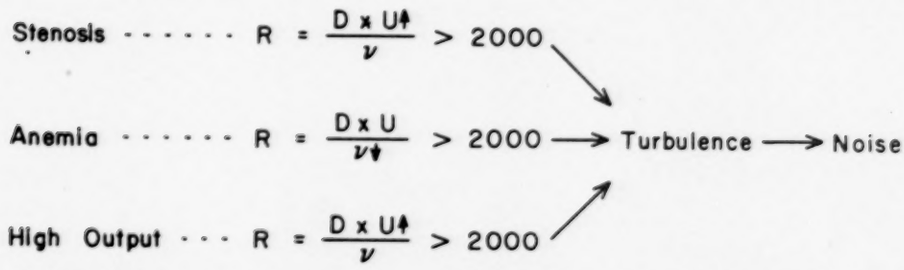


FIG. 1. Diagrammatic representation of the classic theory that murmurs are due to turbulence, where D is the diameter of a tube, U the velocity of the flowing fluid and γ the kinematic viscosity. Arrows indicate the increase or decrease of the values under various conditions. The assumed direct relationship between turbulence and noise is shown.

noise. This interpretation is contrary to the nature of turbulence.

As will be shown later, the conceptual weakness of the turbulence theory does not preclude the possibility that murmurs could be due to this cause. However, for many years there was no dynamic theory recognized by physicists which would explain how the energy and momentum exchange found within turbulence could be translated into acoustical energy [*2*]. That is, the mechanisms whereby the very complex motions of a turbulent fluid would somehow appear as sound were unknown.

Turbulence and Sound. If a relationship between turbulence and sound could be established it might be possible to evaluate the turbulence theory of murmurs in this light. Such a relationship has been constructed recently, in spite of the enormous complexities of the problem. Lighthill [*3,4*] found that a certain portion of turbulent energy would indeed appear as sound if the velocity of the flow were sufficiently high. Lighthill's model of turbulence can be fitted most easily to a description of the sound field one would expect from an unbounded air jet issuing into a large region of still air. However, it can be applied in a broad sense to turbulence in blood. By calculation we found that blood must attain a velocity of at least 2,000 cm./second before any appreciable noise could be generated (see Appendix). As this velocity is never experienced it is evident that some modification must be considered before one can accept turbulence as a cause of murmurs. Now, Lighthill's treatment was not only exact but it was also general, and this has led both to repeated experimental confirmation of his theory and the development of important extensions of it.

Curle [*5*] was able to describe the influence that solid boundaries have upon the sound field generated by turbulence. The essential difference from Lighthill's model is that the boundaries react effectively with the turbulent forces to establish a different type of sound generation. With this, a more efficient conversion of turbulent energy to acoustical energy was realized, provided the boundaries were rigid and the flow took place at low Mach numbers. As the walls of the heart and great vessels are nearly rigid and blood flows at a low Mach number (approximately .004)* it may be that turbulence could theoretically cause murmurs. However, even if one assumes as generous a figure as 500 cm./second for the velocity of the blood, and the point of listening as only 5 cm. from the flow (a distance much less than that described by Curle in his formulation) it is found that about 1 by 10^{-5} dynes/cm.^{2} of acoustical force is produced. As this value is well below the threshold of audibility [*6*] one is even less inclined to accept turbulence as a cause of murmurs (see Appendix).

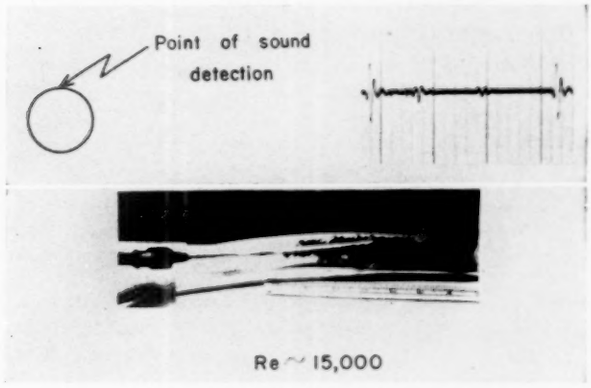
Another important consideration is whether or not the turbulence is fully developed. (This may be more exactly stated as whether or not the turbulence fills an enclosed space or has diffused throughout the boundary layer.) At first glance one might expect a wholly turbulent region to be more capable of producing sound than one in which the turbulence is less widespread. However, Phillips [*7*] has shown that only a region of growing (that is, inhomogeneous) turbulence is

* The Mach number may be defined as:

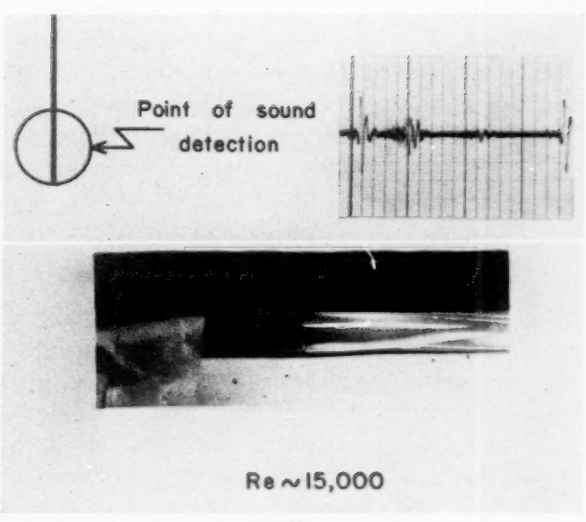
$$\frac{\text{a typical velocity of the fluid}}{\text{the velocity of sound in the same fluid at rest}}$$

or

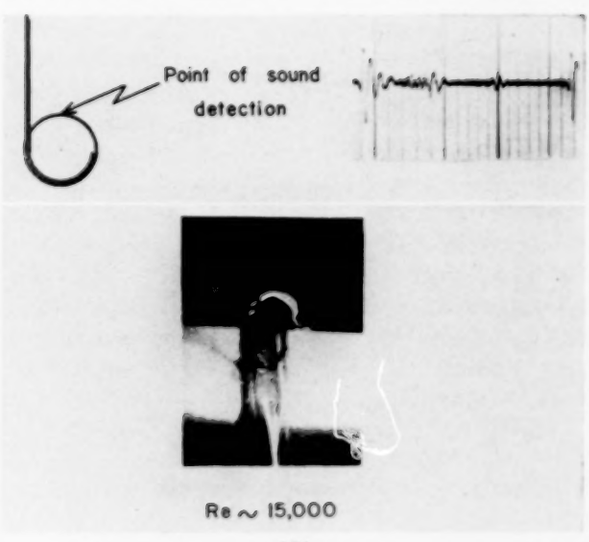
$$\frac{U_0}{a_0}, \text{ i.e., } \frac{500 \text{ cm./second}}{140{,}000 \text{ cm./second}} \sim .004$$



(A)



(B)



(C)

FIG. 2 The development of noise as it relates to the placement of an obstacle in the stream. The large amplitude, low frequency vibrations are thought due to the closure of the valve of the pump and to the sudden distention of the tubing. In (A) no flow noise is produced even though the critical Reynolds number (Re) is greatly exceeded. Immediately after the oscillographic record was obtained India ink was allowed to flow into the stream, thus outlining the turbulent motion of the fluid. A light streak obscures the central axis of the cloud so produced. In (B) and (C) the placement of the obstacles which cause the wake to fluctuate and the records of the noise that this produces are shown. The listening point was approximately 6 cm. downstream from the obstacle.

able to react effectively against rigid boundaries and produce sound. Thus the instant blood becomes wholly turbulent (providing that turbulence is homogeneous in planes parallel to the wall) one should not expect turbulence to behave as an efficient generator of sound. It has been shown that blood becomes turbulent very early in systole [*8*]. Therefore, even if turbulence in blood distal to a valve could generate audible noise, one would expect it only during a brief period in earliest systole. A listener might well interpret this as a heart sound and not as a murmur.

One more modification must be evaluated. Should turbulence be able to cause the solid boundary to vibrate, then it would seem that some significant portion of the energy generated by turbulence might appear as a vibration of a containing wall [*9*] (such as the aorta distal to a stenosis). This represents a most efficient type of sound generation. This assumes, however, that the mass of the wall is small, for otherwise too great an amount of the available energy would be consumed in setting the wall in motion. It also assumes that a large portion of the pressure fluctuations of the turbulence occurring *at* the wall will be transmitted as sound. Willmarth [*10*] has ingeniously shown that the wall pressure fluctuations in a turbulent boundary layer are of considerable strength. However, the work of

Weyers [*11*] indicates that only small acoustical intensities are produced outside the fluid. For example, only 0.26 dynes/cm.^{2} were measured at a distance of but 6 mm. from a very thin-walled (0.025 mm.) plastic tube with air velocities of 4,500 cm./second.

In view of these considerations it seems permissible to state that even under the most favorable conditions it is theoretically unlikely that turbulence in blood will generate any significant acoustical energy which we could detect as murmurs. It now remains to demonstrate this, as follows.

Experimental Results. Pulsatile flow of water and blood was established by the use of the Melrose extracorporeal circulation machine. Initially a plastic tube (Tygon), which had an inside diameter of 1 cm. and a wall thickness of 2 mm., was fitted to the pumping section. Later long segments of latex rubber tubes were inserted in the circuit. These had wall thicknesses of 0.6 and 0.9 mm. and an inside diameter of 1.6 cm. during the systolic phase of the pumping. Sound was recorded by placing a Bowles chest piece directly on the tubes and connecting it by a well fitting plastic tube to the microphone of a Sanborn Twinbeam oscillograph. The sections of the tubes used for sound detection were at a distance of at least 15 feet from the pump outlet so as to avoid being in the considerable sound field generated by the lack of smoothness of the junction.

At Reynolds numbers of flow well above the critical value no murmurs were heard or recorded. (Figs. 2A and 3.)

The experiments were so designed that any significant noise that may have been generated by turbulence would have been demonstrated. By placing the diaphragm of the Bowles chest piece directly on the surface of the tubing, ideal acoustical coupling was obtained. Furthermore, by employing elastic tubes of wall thickness and mass less than found in the aorta or large arteries the transmission of turbulence pressure fluctuations would be favored.

The Role of Cavitation. Before proposing a new theory of the cause of cardiovascular murmurs another possible source of sound in *liquids* should be briefly considered. For many years it has been known that when a liquid is exposed to a pressure approximating the vapor pressure bubbles will form and collapse within a brief period of time [*12*]. This phenomenon is termed cavitation. When blood flows through a stenosis it is possible that such a low pressure will develop. As both the volume pulsations [*13*] and the collapse [*14*] of cavitation bubbles are efficient generators of sound we sought to investigate whether or not cavitation could be accepted as the cause of murmurs. Experiments were performed which demonstrated the presence of cavitation in flowing blood and water passing through plastic and glass tubes of varying shapes and degrees of narrowing [*15*]. We have been unable, however, to demonstrate the phenomenon in experimental animals. It should be mentioned that our experimental results indicate that cavitation will not develop in flowing blood unless the driving pressure is of the order of 350 mm. Hg. Furthermore, its appearance is more likely if there is a roughened plane surface, executing large amplitude oscillations, in a region of high velocity flow. An example of this might be the opening and closing phases of a valve which is stenotic but not completely rigid, and which has led to the development of extreme ventricular hypertrophy. (Another report will describe this work more fully.) It is immediately evident that the restrictions imposed exclude

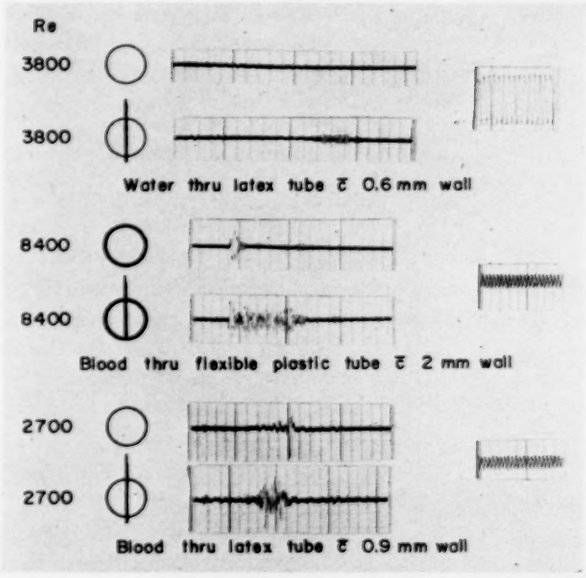


FIG. 3. Records of the production of flow noise by the placement of an obstacle in the stream. The Reynolds numbers (Re) of flow always exceeded the critical value. Other than the low frequency sounds due to valve closure or distention of the tubing wall, no noise is produced even though both blood and water were turbulent. However, the existence of a vortex generating structure in the flow does lead to the production of noise. Varying the fluid or tubing does not alter the results. Reference instrument sensitivity appears on the right. A No. 18 needle was the obstacle used for the last record.



FIG. 4. Diagrammatic representation of the wake beyond a cylinder. The direction and relative strength of both the lift and drag fluctuations are shown.

cavitation as a general cause of murmurs. This necessitated further search for an explanation of murmurs.

AEOLIAN TONES AND FLUCTUATING WAKES

It is evident from the preceding considerations that neither the classic explanation (turbulence) nor a more recent theory (cavitation) is acceptable as a general cause of murmurs. And yet murmurs are audible when blood flows at velocities much less than those required by these theories. The problem may be solved by considering another characteristic of flowing fluids. It is well known that if an obstacle is placed in the path of a fluid a wake will be generated. If this obstacle is a wire (or a cylinder), pressures in the wake will fluctuate in such a manner that a sound and at times a tone is produced. This knowledge was employed by the ancients in constructing Aeolian harps which when placed in the wind produced tones. Should the wire be rough or of inconstant diameter the sound produced would be a noise and not a clear note.

A significant characteristic of this instrument is that it is not necessary to set the strings in vibration by plucking. Nor is it necessary for the strings to oscillate in response to the fluctuating wake for a sound to be generated. This means that the sound can be generated by fluctuations of the wake alone and may thus be considered as purely aerodynamic in origin [*16*]. As will be shown later, the same type of sound generation is realized in liquids and it can thus be readily applied to flowing blood. This point is emphasized because it is important to understand that the generation of murmurs can be explained by wake fluctuations, as in Aeolian tones, and that any vibrations of the containing structures of the cardiovascular system are *secondary* to these forces. This indicates that theories of murmur generation which require vessel wall vibration as an integral part of the explanation very probably are invoking an effect rather than a cause. The noise produced by a nearly periodic wake is transmitted through the vessel wall or myocardium, but its *source* is within the blood itself.

It should be explained that the term Aeolian tones is meant to include sounds which are produced by the same mechanism but which may not be a pure note. Among physicists, for purposes of investigation, it was desirable to design apparatuses such that a single frequency would be produced. It was found that slight variations in the diameter of the wire or cylinder would generate sounds composed of many frequencies (e.g., noise). The same type of fluid flow pattern is developed and the same order of efficiency of sound production is realized even though the obstacle which generates the fluctuating wake is imperfect; thus it is necessary for the obstacle to conform only approximately to the shape of a cylinder. It will be shown later that anatomical deformities which are known to produce murmurs do so conform.

The fluid motion involved in the production of Aeolian tones may best be described in a stepwise fashion. As fluid flows past a cylinder it has been noted that vortices are shed alternately from each side of this cylinder, if one views the pattern two-dimensionally. This leads to the development of a wake which is composed of essentially parallel rows of vortices, which more or less maintain the same alternate positions that were established when they were shed [*17*]. They make up what is termed the von Karman vortex street or trail.

It has been found that the fundamental frequency of an Aeolian tone is that of the frequency of shedding of a pair of vortices. Each pair of vortices leads to the generation of a lift fluctuation in the wake, and the energy of this is characteristically radiated in a direction perpendicular (or normal) to the direction of the flowing fluid. Furthermore, with the shedding of each vortex (not pair) a drag fluctuation is experienced and this has a favored orientation in a direction parallel to the flow. It should be emphasized that the frequency of the drag fluctuation is twice that of the lift [*16*]. Also, the lift fluctuation is much greater than that of the drag. (Fig. 4.)

It might be supposed that the pattern described would not develop once an increased velocity of flow led to the development of turbulence. That is, one could reasonably expect that turbulence would so dominate the flow that the non-random motion of the wake would be overwhelmed. However, Roshko's [*18*]

findings (and the work of Nisbett, described by Phillips [*19*], confirms this) indicate that vortices are shed (and the wake fluctuates periodically) to at least R = 200,000. This is a surprising finding and it is one of great importance. It means that even in a region of turbulence a cylinder (or analogous structure) can cause vortex generation. This results in a wake pattern which is *not* random but which fluctuates in a nearly periodic fashion. It may be concluded that in the range of velocities (and, hence, of Reynolds numbers) in flowing blood, the presence of a structure capable of generating vortices would lead to a greatly increased order (or decreased randomness) in the motion of fluid particles. From this one can expect a greatly increased efficiency of sound production. This conclusion may perhaps be regarded as the central theme of this theory of the production of murmurs.

It is true that an extended vortex trail does not persist under these conditions. But, as explained by Yudin [*20*], the radiation of energy is completed at or shortly after the shedding of each vortex pair and prolonged persistence of the vortex trail contributes nothing to the generation of acoustical energy.

The Intensities of Aeolian Tones. Before one can accept the theory that cardiovascular murmurs are due to wake fluctuations generated in the manner of Aeolian tones it is necessary to be sure that sufficient acoustical energy is produced by this type of flow. This is only reasonable for it was essentially the failure of turbulence, under the conditions of blood flow in the body, to generate audible sounds that led to its rejection as an explanation of murmurs.

Aerodynamicists earlier investigated the intensities of Aeolian tones and their results have shown a remarkable agreement [*20,21*]. More recently others [*16,19*], employing Lighthill's theory, have derived formulas which are very similar to Curle's for turbulence in the presence of solid boundaries. It might be supposed that unreasonably high velocities of blood flow would then be required before appreciable sound was produced. However, these formulas were developed for those cases in which the point of listening is a great distance from the flow (the order of a typical wave length). Gerrard [*22*] has published an experimentally derived formula from which intensities may be determined for the near or intermediate field, and it is in this region that one detects murmurs. By application to flowing blood one could expect an (audible) acoustical force of 5×10^{-2} dynes/cm.^{2} at a velocity of 150 cm./second and at a distance of 5 cm. from the flow (see Appendix). As these values are reasonable, it is possible, from theory at least, for blood undergoing wake fluctuations to lead to sound intensities that we could hear.

Experimental Results. The apparatus described previously was used. Measured outputs were the same. By placing the straightened end of a paper clip across the stream, sounds were heard and recorded which bear a close resemblance to murmurs.

It might be supposed that free flow must be possible on both sides of the wire before a vortex pattern could be generated. However, we postulated that if vortex shedding occurred along one side of the length of the wire, then essentially the same wake pattern would be produced and this would lead to sound. The other end of the same paper clip was appropriately shaped into a curve which could be pressed flush against the inner wall of the plastic tube. A length equal to half the inner circumference was chosen so as to avoid any configuration similar to an orifice (it will be shown later that orifice flow is a special case of wake fluctuation). As before, a murmur was heard and recorded. (Figs. 2B and 2C.) Experiments performed with very thin-walled elastic tubes, using blood or water, produce similar results. (Fig. 3.)

All the experiments were repeated with the listening area submerged in a tank of water so as to exclude the possibility that aspiration of air contributed to the sound produced. The results were exactly the same.

It should be noted that the area of the paper clip or needle is small in comparison to the cross sectional area of the tubes and thus demonstrates that such an obstruction is a relatively efficient generator of acoustical energy. Furthermore, it is not necessary that the obstacle be circular for, as shown by Fage and Johansen [*23*], the same vortex pattern develops downstream of a thin flat plate.

ORIFICE FLOW

If the wire placed halfway around the inside of the plastic tube is now considered to be a complete circle, it will be obvious that an orifice of great diameter has been constructed. If the thickness of the wire is increased the diameter of the orifice will become smaller and smaller. It is evident that fluid flowing over these obstructions will develop roughly the same type of vortex

generation and wake fluctuation as has been previously shown. When the diameter of the orifice is large it is to be expected that the frequencies of the noise or tone will be determined by the thickness of the wire and the velocity of flow. When the diameter of the orifice is small the frequencies of the noise or tone will depend on the diameter of the orifice itself and the velocity of the flow. If the wire is modified (flattened) so that in the first case it resembles a washer placed in the stream and in the second a circular plate with a small hole in the center, the basic configuration required of a vortex generating structure is not altered. It should be noted that unless the orifice is symmetrically and smoothly constructed, noise rather than a clear note will be produced.

The effects of the geometry of this type of obstruction must be considered further as the diameter of the orifice relative to the diameter of a tube in which it has been placed has some bearing on the basic frequency produced. Thus, if the orifice diameter almost equals that of the tube, the frequency will be approximately determined by the Strouhal relationship: frequency $\sim \frac{\text{velocity of fluid flow}}{6 \times \text{width of orifice shoulder}}$. This is usually written $N \sim \frac{U}{6d} \sim \frac{.17U}{d}$. It can be seen that if the orifice diameter becomes smaller the value d will increase and the expected frequency of the murmur will be lower. However, when the diameter of the orifice is very small then a new relationship can be roughly applied: $N \sim \frac{.6U}{d}$, and a higher frequency for a given velocity of flow can be expected. Thus, as a constriction or stenosis becomes greater (orifice diameter decreases) one should find that the basic frequency, at first high, will become lower and then increase once more. This can be applied to the frequency or pitch of murmurs heard clinically. With the high frequency murmurs associated with high output states the blood passes over the relatively narrow width obstructions caused by the valvular ring or the attachments at the base of the valve. The lower frequency murmur associated with a valvular stenosis might well be due to the increased width of the orifice shoulder found in such a case. The high pitch of the murmurs of aortic and pulmonic valvular insufficiency is understandable as the blood must pass through what is often a small central orifice which is the only aperture remaining after almost complete apposition of the valve leaflets at the beginning of diastole.

The fact that a small circular orifice will produce relatively higher frequencies for a given velocity of flow is one that must be borne in mind. It has been stressed by Anderson [*24*] that a misconception has developed in the physical literature in that it has been erroneously assumed that fluid flowing through a slit which has a diameter equal to that of a circular orifice will produce a sound of the same frequency. This is not the case, however, and Johansen's [*25*] study of vortex shedding at relatively low velocities of flowing water suggests that one may expect a higher frequency when dealing with circular orifices. As already noted this has some significance when one considers the unusually high frequencies of the murmurs of aortic and pulmonic insufficiency.

When the diameter of an orifice decreases it is not known at what point the frequency becomes dependent upon its diameter rather than on the width of the shoulder. Spivack's [*26*] experiments concerning parallel cylinders placed in an airstream suggest that this might occur when the orifice diameter becomes equal to the width of the shoulder, but this is only speculative.

These characteristics of orifice flow are summarized in Figure 5. It is to be expected that the actual frequencies will be higher than those shown. This is because vortex shedding from each side of the orifice shoulder is not possible, and the irregularities on the surface of a diseased valve will behave as separate small width obstructions (hence, produce high frequency noise) and contribute these components to the sound field. Furthermore, the velocity through the orifice will increase as the diameter decreases, and this will lead to higher frequency noise.

Another characteristic of this type of flow must be presented. When fluid flows through a circular orifice in a thin plate it has been found that annular vortices are shed much as when one blows smoke rings. The basic frequency of the sound that may be produced equals the shedding frequency [*27,28*]. If the orifice plate caps the downstream end of a tube there is a strong tendency for the shedding frequency to be heard upstream. However, a short distance downstream from the orifice it has been found that the vortices will often coalesce. Hence if one

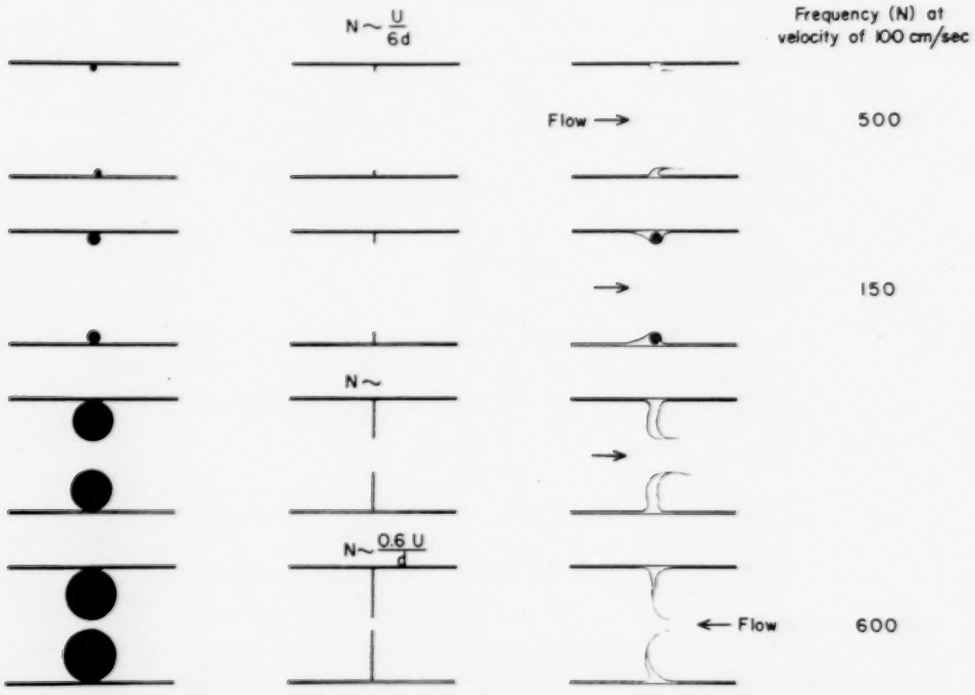


FIG. 5. Diagrammatic representation of the basic structural similarity between an encircling curved wire, an orifice, and valvular deformities as may be found in the body. The theoretical frequencies are shown on the right. The third row of diagrams shows a relationship for which it is unknown which of the two formulas apply. Probably it is that shown above the lowest line of diagrams. See text.

listens in this region a sound is heard which has a frequency less than that of the shedding frequency. These considerations are illustrated in Figure 6 and the suggestion is made as to how this resembles the conditions found in the body. Thus one might expect the murmur of aortic stenosis to be lower in frequency when listening over the aorta, or aortic area, than when listening over the apex of the heart. This frequency differential is especially marked when one places the stethoscope directly on the aorta and myocardium at operation.

This tendency for downstream vortex coalescence has been established only for flow through a circular orifice. There is some reason to expect that this tendency would be less prominent for flows over orifice shoulders of small width. In these instances it might be expected that the upstream radiation of the drag pulse would operate to contribute higher frequency components to the pitch of the murmur. Its effect, however, would be less striking than with a small circular orifice. This may be a partial explanation of why the murmurs of high output states have less of a frequency difference relative to the downstream and upstream position of listening. On the other hand, the murmurs of mitral stenosis and insufficiency have a marked difference in pitch. Presuming the blood to pass through a small central orifice in both cases, one would expect the murmur heard downstream with mitral stenosis to be of lower frequency than that heard upstream with mitral insufficiency. (In addition, the higher velocity of flow from the left ventricle with insufficiency would result in a higher basic frequency.)

Lastly, an observation by Anderson [*29*] warrants mention. He found that different sound frequencies were produced when a fluid flows through the same orifice in different directions. The reason for this is unknown, and speculation as to the cause results only in mystification. It is noted only in that it may have some bearing, in addition to the variations in pressure and in velocity, on the marked frequency difference detected in the murmurs of aortic stenosis and insufficiency.

The Effect of Streamlining. If the orifice is considered to be streamlined so that it assumes the shape of a Venturi tube, then several modifi-

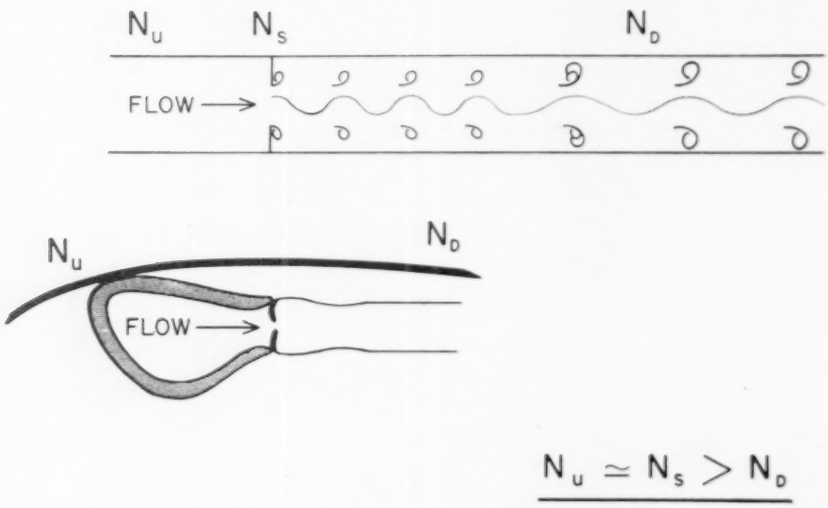


FIG. 6. Schematic representation of the changing frequency of the fluctuating wake due to vortex coalescence. N_u stands for the upstream frequency, N_s the shedding frequency, and N_D the downstream frequency. The upstream frequency is shown as being only approximately equal to the shedding frequency because if one listens directly over the orifice a great deal of the low frequency downstream components are transmitted to this point along the tubing wall. The diagram of the heart indicates how, when one listens over the apex and base of the heart, one is over the upstream and downstream frequency fields respectively.

cations of the noise may be expected. The point of vortex shedding will move downstream from the point of least diameter, that is, the throat. For this reason, the effective width of the orifice shoulder becomes less. As a result, the frequency of the noise will be higher for flow through an opening of given diameter. In addition, the acoustical intensity will be less because it is dependent in part on the area that an obstacle presents to the flow (see Appendix).

Experimental Results. Steady flow of water from the tap was used. Holes of various diameters were drilled in the aluminum protective caps found on standard vials of liquid drugs. These were placed snugly over the end of a plastic tube, and then fitted into the free end of another tube of the same material. The relationship of pitch to orifice size previously described herein could be demonstrated by auscultation. In other experiments records were obtained of the difference in frequencies found upstream and downstream from an orifice. For these a Bowles chest piece was placed on the tubing wall. This was connected to the microphone of an Elema phonocardiograph. The results are shown in Figure 7. The virtual absence of low frequency components in the murmur located upstream of the orifice is shown. As expected, noise rather than a clear note was produced, as the holes drilled in the aluminum caps were not finely machined. It must be pointed out that the apparatus utilized for frequency analysis is much less advanced than that used in most acoustical research. However, the discrimination is at least comparable to that which one would be able to make when listening with a stethoscope and therefore suffices for this study of murmurs detectable clinically. The use of the same tubing both upstream and downstream helps to point out again that the characteristics of murmurs are not as dependent on the vibration of containing structures as has been previously supposed but appear to be more closely related to the regional behavior of the fluid. That is, the fluid mechanics of murmurs appear to be the more significant determinants of their characteristics.

Demonstration in Animals. The first demonstration was designed to show the changing frequency of a murmur as the diameter of an orifice or stenotic region varies. A mongrel dog was anesthetized with a barbiturate, placed on a respirator, and the heart exposed. A constricting plastic sling was placed a few centimeters distal to the aortic valve. Sound was recorded by placing a plastic tube flush on the aorta at a point just beyond the constriction. This tube was again connected to the microphone of an

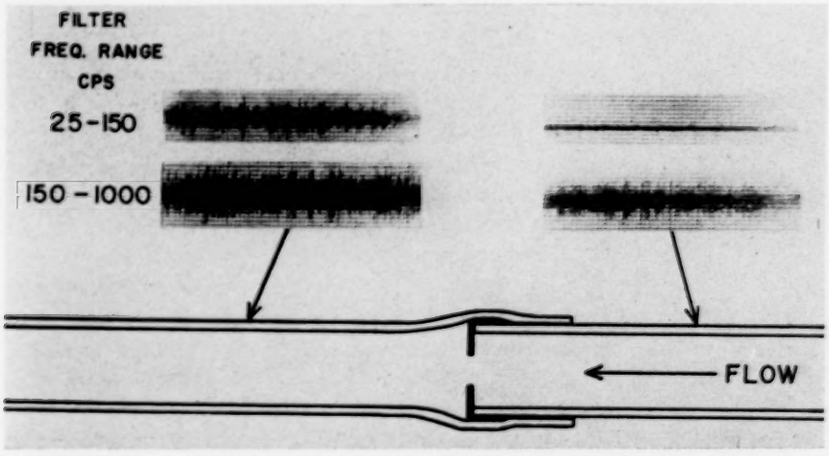


FIG. 7. Records of the frequency spectrums found above and below an orifice are shown on the diagram. The virtual absence of low frequency components upstream is striking. The orifice plate used was much thinner than shown here graphically.

Elema phonocardiograph. Widely separated frequency bands were selected for comparison tracings. The results are shown in Figure 8. As the constriction was increased from slight to maximal the relative contribution of the higher frequency components of the murmur, at first dominant, became less pronounced and then reappeared more strongly. It appears to us that the varying pitch of the murmurs so produced is analogous to the varying pitch of the murmurs associated with high velocity flow through a normal valve, moderate to severe valvular stenosis, and valvular insufficiency respectively.

Another dog was similarly prepared. A moderate constriction was placed. By the technic just described a demonstration of the changing frequency components as related to the position of listening was attempted. The results are shown in Figure 9. As anticipated, it was found that the frequency of a murmur becomes higher as the point of listening moves from a position perpendicular to the flow and downstream from a constriction, to one parallel to the flow and upstream.

COMMENTS

The results of recent investigations of the relative intensities of acoustical energy produced by turbulence and periodic wakes have proved to be of great help in the development of this theory. Until it was shown that turbulence associated with low velocity flow is an inefficient generator of sound it was not possible to evaluate correctly its role in the production of murmurs. The more recent demonstration that periodic wake fluctuations exist even at very high Reynolds numbers is another convincing reason for considering this type of flow rather than turbulence as the probable cause of murmurs. Not having the advantage of these findings Bondi [*30*], who placed due emphasis on vortex generation especially where the vessel caliber changes, was unable to distinguish clearly between the two types of flow. In the medical literature the concept grew that the likelihood of vortices being shed at abrupt obstructions leading into dilated vessels was tantamount to saying that turbulence, and hence murmurs, would be more likely to develop in such a region. An example frequently given was aortic stenosis in association with poststenotic dilatation. However, the distinction between turbulence and periodic wakes is an

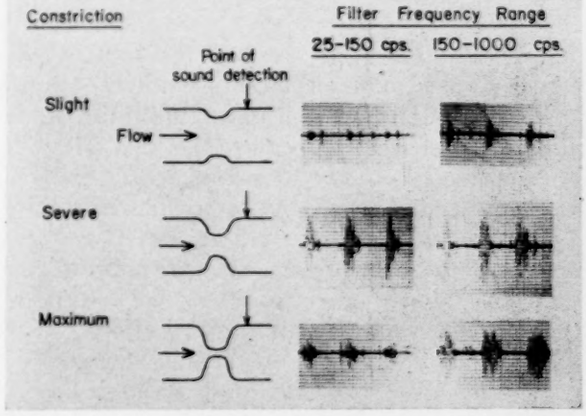


FIG. 8. The changing frequency spectrums of murmurs produced in the aorta of a dog with increasing degrees of constriction are shown.

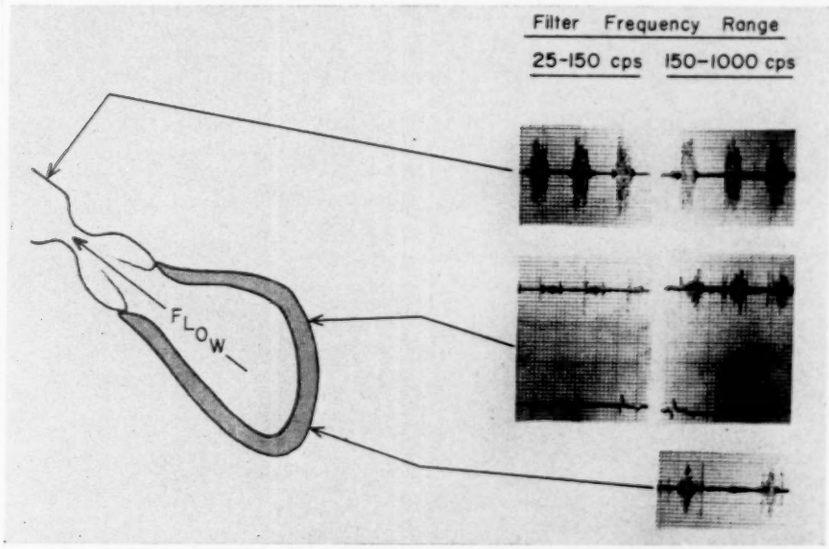


FIG. 9. Records of the change in frequency spectrums of murmurs produced by moderate constriction of the aorta of a dog as these relate to the position of listening are shown. An electrocardiogram accompanies the second row of sound records. It was only possible to obtain the record from the apex by increasing the force of systolic discharge by the administration of epinephrine.

important one, as has been shown by von Karman [*31*]. Roshko's [*18*] work with air flows clearly indicates that both types of flow can develop independently. Indeed, at high Reynolds numbers, even though the vortices are composed of turbulent fluid, they are *nonetheless shed periodically*. This results in a sound field which is dominated by discrete noise rather than the broad spectrum noise that would be caused by turbulence. Our experimental results indicate that the same holds true for liquids.

It has been speculated that musical murmurs might be generated by blood flowing past chordae and may thus be likened to Aeòlian tones. We believe that this is an unnecessarily restricted view of the phenomenon. As has been mentioned before, Aeolian tones are but the most easily investigated form of periodic wake fluctuations. It was apparently not realized that the wake fluctuation generated by this type of flow is but the simplest form of what occurs downstream of any appropriate obstacle or orifice-like structure. Thus, Aeolian tones are not restricted to pure notes, as the interpretation cited implies, but may be utilized to explain the mechanism of many types of periodic or nearly periodic wake fluctuations. We sought to demonstrate this by presenting the experimental findings as a progression from the simplest to the more complex flows.

The fact that musical murmurs are heard at all is surprising when one considers the lack of smoothness and symmetry of the obstacles through or around which blood must flow. Their occasional detection under physiological conditions is suggestive evidence that the expectation of nearly periodic wakes causing most murmurs is a reasonable one.

As mentioned earlier, it is the periodicity or near periodicity of the wake which allows one to accept wake fluctuations as an acceptable cause of cardiovascular murmurs. For it is this nonrandomness which permits a relatively efficient transfer of the energy of local fluid motion into perceptible acoustical energy.

If turbulence were indeed the cause of murmurs then all murmurs should have essentially the same frequency. This expectation is based not only on what one might postulate knowing that turbulent motion is random, but also on Lighthill's study [*3,4*] and several experimental confirmations of his prediction that the frequency spectrum of noise due to turbulence is very broad.

It should be re-emphasized that the vortices themselves do not contribute to the sound field. This has been stressed by Yudin [*20*], who points out that they are wattless. What causes the pressure fluctuations in the wake is the flow of fluid from other areas (the opposite side of the cylinder in the case of Aeolian tones) to fill the space that was occupied by the vortex just prior

to its being shed [*16*]. It is not the *presence* of vortices (or of "many eddies") at the region of an abrupt obstruction such as a stenosed valve which leads to sound, as has been suggested [*32*], but rather the *response* of the mass of fluid comprising the wake to the shedding of the vortices.

By considering murmurs as due to nearly periodic wake fluctuations, a unity is offered to the many divergent characteristics of murmurs as they are known clinically.

The intensities and frequencies of murmurs are those that would be expected from nearly periodic wakes. This does not hold true for cavitation or turbulence. The very fact that thrills often accompany murmurs suggests that a mechanism capable of efficiently producing vibrations of moderate frequency must exist. Nearly periodic wake fluctuations would provide such a mechanism.

This theory, furthermore, helps to explain the variation in the pitch of a murmur as the listening point moves from a position normal to and downstream from a stenosed valve to one parallel and upstream. Thus the murmur due to aortic stenosis or sclerosis at auscultation is higher in frequency or pitch at the apex than over the aortic area. In the case of the murmurs of mitral stenosis and insufficiency, one can expect the latter to be higher in frequency because one listens upstream, and hence out of the region of vortex coalescence; also, the primary shedding frequency is higher as a result of the higher velocity flow from the left ventricle.

Some understanding of one's ability to localize murmurs is gained from this theory. The fact that a listener often is able to identify the diseased valve by noting the site in which it is heard most easily is of great help in diagnosis. According to this theory one would expect that low frequency murmurs of relatively great intensity would be largely confined to the region closely downstream of the stenotic valve. This indeed seems to be the case in aortic and pulmonic stenosis, as the location of the murmur (and at times of a thrill) on the chest wall is often found to be immediately above these regions. The rather frequent transmission of the murmurs of aortic stenosis and sclerosis to the neck can be explained by the recent findings about the nature of wave propagation along fluid-filled tubes [*33*]. It has been found that flexural wall vibrations (that is, radial vibrations) are well transmitted along liquid-filled tubes. This means that once the vibrations of the murmur are impressed on the aortic wall they will travel along this wall with only moderate attenuation. Thus one is not surprised to find that a thrill will accompany the murmur in the neck, a physical sign often noted.

It has already been mentioned that the obstruction does not have to be very large in order to produce significant noise. This characteristic of wake fluctuations generating acoustical energy might be applied to our understanding of the presence or persistence of some murmurs. Thus, the Carey Coombs murmur heard at the apex in association with minor deformities of the mitral valve is understandable on this basis. This seems to apply also to the murmurs associated with high output states or with the murmur of aortic sclerosis when found to be associated with relatively minor alterations of the valve bases [*34*]. The flow murmur at the pulmonary area with atrial septal defect is another example.

Again, one is not surprised to find that a murmur will still be detectable after successful valvulotomy for often there remains a significant portion of the valve which is capable of generating a fluctuating wake. One wonders whether or not the catheters used with intracardiac microphones are sufficient in size to contribute to the noise recorded. If so, this must be reckoned with.

It can be seen from the Appendix that the intensity of the sound produced by fluctuating wakes will vary as the fourth power of the velocity of the flow. One can expect, therefore, that the loudness of a murmur will increase rapidly for relatively small increases in velocity. As blood must pass through stenosed areas which vary widely in cross sectional area a resultant wide range of velocities may be expected. It seems reasonable that an even greater range of sound intensities will be produced. Thus the wide range of the loudness of murmurs detected clinically appears reasonable when viewed in this light.

Several broad applications of this theory appear possible. It seems to us that the behavior of the fluid is represented remarkably well by the acoustical phenomena produced. When better technics of analyzing the frequency of murmurs are applied, it may well be possible to gain a fairly accurate picture of the physical values which describe the flow simply from the nature and characteristics of the sounds produced.

In addition, knowing the forces involved in any region of the cardiovascular system, it may

be possible to offer some insight into the degenerative processes to which the system seems to be so prone. In this connection, it has been possible to propose a new theory of the cause of poststenotic dilatation which takes into account the focal periodic stresses which characterize wake fluctuations. We hope to report on this in the near future. In the design of extracorporeal machines it may be helpful to incorporate knowledge of the fluid mechanics of blood flow so as to prevent or decrease tissue and cellular damage. This consideration applies more strongly in the case of valvular and vascular protheses.

SUMMARY

It is suggested that the classic theory that murmurs are due to turbulence in flowing blood is unlikely to be correct, as is another theory that they may be due to cavitation. A new theory concerning the cause of murmurs is offered. The postulates of the theory are:

1. The bulk of the acoustical energy in murmurs is due to nearly periodic fluctuations in the wake found downstream of any appropriate obstacle and the characteristics of this type of flow are similar to those associated with Aeolian tones or orifice flow.

2. The vast majority of murmurs are due to protuberances of minor to moderate size, to wall discontinuities of the heart, its valves and the larger vessels. These murmurs are greatly intensified by relatively small increases in the velocity of flowing blood.

3. The position of listening as it relates to a column of moving blood modifies the perceived frequencies to a remarkable degree.

4. Application of this theory to the known diverse characteristics of murmurs lends a unity to the understanding of their peculiarities.

5. The behavior of blood flowing around and beyond any obstacle capable of generating a murmur is faithfully represented by the acoustical characteristics of the murmur so produced.

6. Knowledge of the forces involved in nearly periodic wake fluctuations allows more complete understanding of the stresses that may lead to degeneration of cardiovascular structures.

APPENDIX

The physical and mathematical basis on which this theory rests will be very briefly stated.

Lighthill [*3,4*] pictured the source of sound in a turbulent jet as being an array of acoustical quadrupoles. Amplification is noted in the region of shear which behaves like an "acoustical sounding board." Most of the energy is radiated in a direction making an acute angle with the jet. The intensity may be represented by the much simplified formula

$$I_x \sim \rho_0 \frac{U_0^8}{a_0^5} \frac{L^2}{x^2} f(R),$$

where I_x is the intensity of the sound at point x, ρ_0 the density of the fluid at rest, U_0 is a typical velocity of the flow, a_0 is the velocity of the sound in the fluid at rest, L a typical dimension of the flow, x the distance from the flow to which sound is radiated, and $f(R)$ some function of the Reynolds number. If the velocity of blood is considered to be 500 cm./second, and even though the intensity increases as its eighth power, its value will be very much less than the value [*35*] of the velocity of sound in blood, 140,000 cm./second taken to the fifth power. Even for a gas, in which the velocity of sound is much less than that of a liquid, an insignificant amount of acoustical power is produced for flows less than Mach 0.3.

When a solid boundary (a perfect acoustical reflector) exists in the flow the source of sound is now due to an array of acoustical dipoles [*5*]. The bulk of acoustical energy is now radiated across the flow from the solid boundary and in a direction perpendicular to the flow. The intensity may be described by the formula

$$I_x \sim \rho_0 \frac{U_0^6}{a_0^3} \frac{L^2}{x^2} f(R)$$

Phillips [*7*] has described the intensity of Aeolian tones found at a large distance from the obstacle. This may be represented by

$$I_x \sim \rho_0 \frac{U_0^6 l d}{a_0^3} \frac{S^2}{x^2} \alpha \cos^2 \phi,$$

where l and d are the length and diameter of a cylinder, S the Strouhal number, α a constant which equals approximately 0.037 for turbulent flows, and ϕ is the angle between the direction of observation and the incident stream.

For the near or intermediate field of Aeolian tones Gerrard [*22*] has written

$$I_x \sim \rho_0 \frac{U_0^4}{a_0} \frac{L^2}{x^2} \cos^2 f(R)$$

For the mean square acoustical pressure $\overline{p^2}$, in dynes/cm.^{2}, this becomes

$$\overline{p^2} \sim \rho_0^2 U^4 \frac{L^2}{x^2} \cos^2 f(R)$$

It will be noted that there has been a progressive reduction of the importance of the term a_0. Thus it becomes possible for a reasonable velocity of flow to generate significant acoustical energy.

As the intensity relates to the fourth power of the velocity, small increases of the velocity of flowing blood result in large increases of the acoustical power. The term L^2 is comparable to the terms l and d of Phillips' paper, and hence it is descriptive of the effect that the area of the obstruction has on the intensity of the sound produced. Lastly, the term $\frac{1}{x^2}$ means that the intensity falls off rapidly with the distance that the observer is from the flow. It thus becomes significant when one considers that murmurs are very often found to be well localized.

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Angina Pectoris*
I. A Variant Form of Angina Pectoris

Preliminary Report

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CLASSIC Heberden's angina pectoris is a distinct syndrome with two major characteristics: (1) the pain which is provoked when the work of the heart is increased is relieved by rest or the administration of nitroglycerin; and (2) an electrocardiogram taken during pain generally shows depression of the ST segment in standard test leads I, II, III and V_4, without reciprocal elevation. (Fig. 1A.) There are several other well known clinical syndromes in addition to classic angina which are characterized by anginal pain, but which differ from the classic form in various ways.

There is another type of angina pectoris which appears to be a separate entity, and has not been set apart from the heterogeneous group of anginal syndromes. It does not show the two major characteristics of the classic form and, in addition, has other important clinical and experimental differences. In this variant type of angina the pain comes on with the subject at *rest* or *during ordinary activity* during the day or night. It is not brought on by effort. During an attack, the ST segments are transiently and often remarkably *elevated* and there are reciprocal ST depressions in the standard leads. (Fig. 1B.) The attacks almost always terminate spontaneously, but if long continued they may lead to death. In addition, there are other clinical and electrocardiographic differences as well as important physiological, experimental and chemical distinctions which will be described in this and succeeding papers.

This study is based upon thirty-two cases, twenty of which were personally observed. Three illustrative cases will be presented here; the remainder will be described in a monograph now in preparation.

In his paper on "Disorders of the Breast," Heberden [*1,2*] briefly mentioned non-exertional angina. His description of non-exertional angina is vague and not nearly as graphic as that of classic angina pectoris. It is assumed that some of Heberden's cases in which angina occurred with the subject at rest probably represent the first reported instances of the variant form of angina

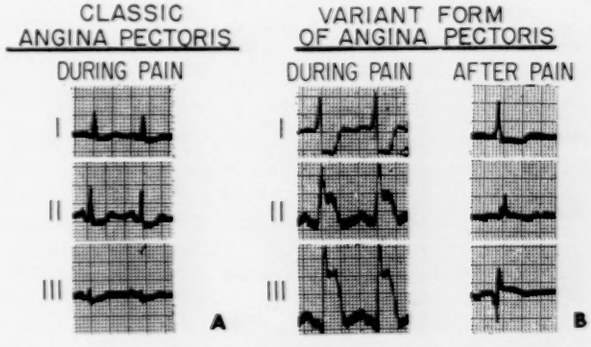


FIG. 1. Comparison of electrocardiographic characteristics of classic angina pectoris and the variant form. A, Classic angina pectoris: ST segments show depression without reciprocal ST elevation. Electrocardiogram obtained after exercise. B, variant form of angina pectoris: During spontaneous pain, ST segments show elevation in leads II and III with reciprocal ST depression in lead I. Immediately after pain, the electrocardiogram retutns to normal or to pre-pain pattern.

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pectoris. This anginal syndrome therefore is properly considered a variant form of angina pectoris.*

REVIEW OF LITERATURE

The problem of non-exertional angina has interested cardiologists over the years. Terms applied have included angina decubitus, spasmodic angina, status anginosus, and angina at rest, among others. When patients with the variant form of angina pectoris were first encountered, the literature was searched for additional cases. Among some 250 articles on atypical angina pectoris, reports were found of twelve patients whose clinical and electrocardiographic pattern, in retrospect, suggested the diagnosis of the variant form of angina pectoris [*3–14*]. These cases, however, were described along with examples of other types of cardiac pain, and often were ascribed to disorders such as myocardial infarction, angina pectoris due to disturbing dreams, tobacco, heart failure and hypoglycemia. In most instances, the electrocardiograms were taken during and after the attacks more by chance than by design. These twelve case reports, together with those of our own patients, will be summarized in the monograph.

This review of the literature was of aid not only in delineating the clinical entity of the variant form of angina pectoris but in bringing out other relevant facts. Angina decubitus itself was found to be a heterogeneous group of ailments consisting of nocturnal myocardial infarction; angina pectoris precipitated by dreams, hypotension or arrhythmias; paroxysmal left-sided heart failure; pre-infarction angina; and the variant form of angina pectoris. The term "angina decubitus," meaning angina of recumbency, has not only been applied to different entities in the past, but cannot be used properly to describe the variant form of angina since in it the pain occurs frequently in non-decubital positions. The term "angina decubitus" should be discarded, along with other inexact diagnoses such as "inflammation of the bowel," "typhoid-malaria" or "acute indigestion." There is danger that the physician, deciding that a condition is angina decubitus, may believe he has made a diagnosis. All he is doing in fact, is applying a scientific sounding term to a heterogeneous group of cardiac ailments. In every case of angina decubitus, diligent and careful observation by the physician should yield a more meaningful diagnosis.

The variant form of angina pectoris is not uncommon. Cases are not diagnosed now for several reasons: (1) Medical students are generally taught that angina pectoris occurs with exertion and recedes with rest. True angina pectoris, therefore, is generally regarded as only that pain which is provoked by exertion or excitement. Many authorities, in fact, refer to the syndrome as "effort angina." (2) Electrocardiograms taken at the beginning or end of a severe attack of the variant form, or during a mild attack, may be unchanged or show spurious improvement. (3) If only one electrocardiogram is taken during pain, myocardial infarction is diagnosed almost inevitably. (4) Physicians are not aware of the complete syndrome, its diagnosis and treatment.

ILLUSTRATIVE CASES

The three typical cases to be presented illustrate most of the essential features of the variant form of angina pectoris, and demonstrate how it differs from the classic form.

Case 1. H. B., a forty-two year old physician, was awakened one morning with rhythmic precordial pressure and pain. Each pain lasted approximately forty-five seconds and recurred at remarkably constant periods of approximately five minutes. He described the attack as consisting of approximately forty distinct cyclic episodes of pressure. The attacks lasted about two hours. They occurred early in the morning and sometimes also in the late afternoon. They recurred at approximately the same time in each twenty-four-hour period. In spite of the severe pain at rest, he was able to play eighteen to thirty-six holes of

* Early in these studies we used for identification of this type of angina the phrases "angina pectoris decubitus," and "a new type angina." Later in lectures and exhibits we used the descriptive term "angina pectoris inversa," since some of the *major* characteristics are opposite to those of the classic form. These terms, however, are unsatisfactory, and at this point in our knowledge, the term "a variant form of angina pectoris" seems preferable although far from ideal. This identifying phrase seems acceptable as long as it is understood that this syndrome is only one of several variants of angina pectoris. "Angina pectoris" will, of course, be used to signify the classic form of the syndrome so lucidly described by Heberden in 1768. The features of this variant form of angina pectoris to be discussed in this paper will be limited to the findings observed in clear-cut cases. In many cases there are confusing combinations of chest pains of various types, such as pain of skeletal origin, anginal pain, and symptoms of a psychogenic nature suggestive of angina. Such cases are not considered here.

golf or ski for as long as four to six hours without any discomfort.

Two days after the onset an electrocardiogram was taken for the first time *during* an attack of pain. This showed marked ST elevation in leads II and III and slight reciprocal ST depression in lead I. (Fig. 2A.) Surprisingly, the ST segments returned to the isoelectric level within one to two minutes after the pain ceased spontaneously. (Fig. 2B.)

He was hospitalized. Physical examination was within normal limits. The same electrocardiographic abnormalities that were repeatedly found in association with the pain disappeared when the pain subsided. Exercise tests were negative. He continued to be awakened by the pain each morning. Continuous electrocardiograms were taken during one attack. During pain, ST elevations appeared. With disappearance of the pain, the ST segment returned to the base line. (Fig. 3A.) It was found also that the recurrent pains and electrocardiographic findings could be terminated by the administration of nitroglycerin. (Fig. 3B.) Hypoglycemia was suspected and the patient was given a high carbohydrate feeding at 4:00 A.M., but this did not prevent the usual early morning attack. Administration of heparin, antispasmodics, sedatives or other drugs had no effect on the symptoms. After his discharge from the hospital on daily heparin therapy, his symptoms continued unchanged. Gradually, restrictions on his activities were reduced.

Six months after the onset of the pain he suffered a typical but mild myocardial infarction, with changes in leads II, III and aVF. These were the same leads which showed ST elevation during his previous attacks of the variant form of angina pectoris. All attacks of spontaneous pain disappeared immediately after the infarction, and have never recurred. This amazing and abrupt cessation of attacks was completely unexpected. At the time of its occurrence it was not understood, but in the light of further experience its mechanism became clear.

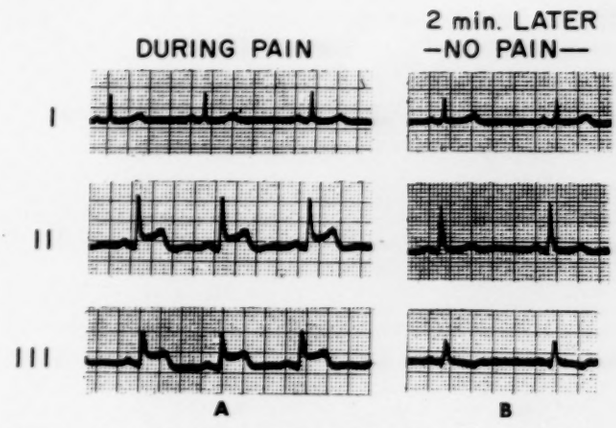


FIG. 2. Case I. Electrocardiogram of variant type of angina pectoris. A, during spontaneous pain. Note the ST elevation in leads II and III and slight depression in lead I. B, two minutes later the pain disappeared and the electrocardiogram reverted to normal.

Comments: This case illustrates several important features. (1) Pain occurred with the patient at rest. (2) There was no pain even with marked exertion. (3) The electrocardiogram was normal in the absence of pain. The physical examination

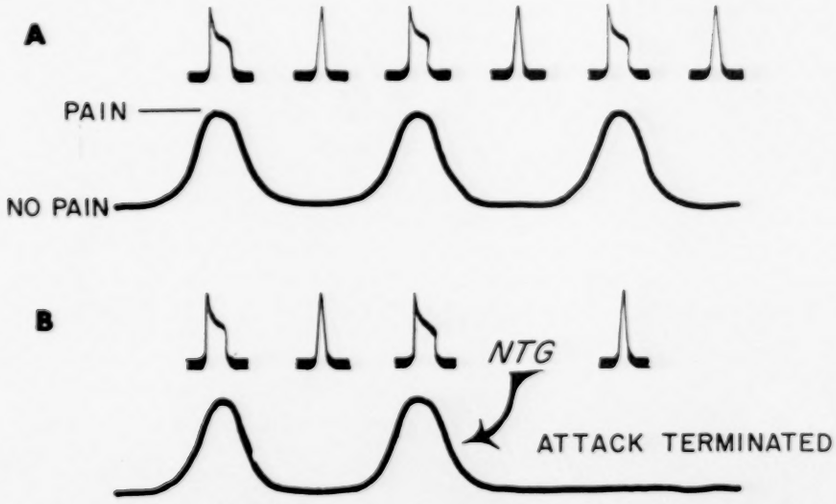


FIG. 3. Case II. Continuous electrocardiographic tracing taken during an attack of angina pectoris variant, together with time-pain curve (diagrammatic). A, pain recurred at remarkably constant intervals of about five minutes. During pain, ST elevation occurred. The electrocardiogram became normal between episodes. As many as forty recurrent episodes occurred. B, the administration of nitroglycerin prevented further cycles of pain and ST elevation.

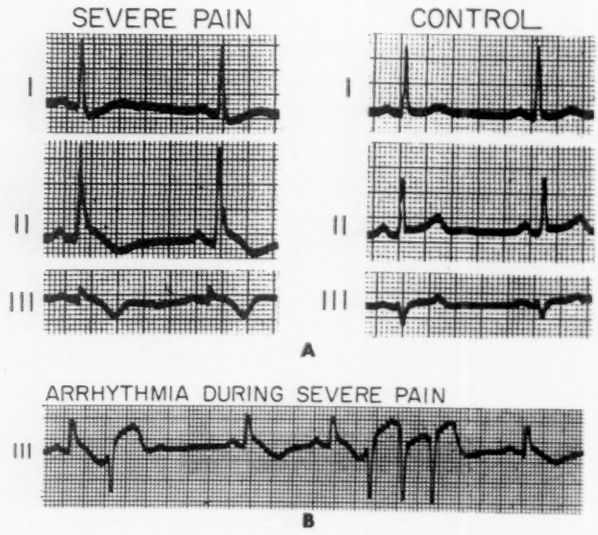


FIG. 4. Case II. Electrocardiogram during a severe attack. A, during severe pain, there is marked ST elevation in leads II and III, and depression in lead I. The R wave greatly increased in height and width in the same leads that showed ST elevation (particularly in lead II). Control tracing taken a few minutes later after pain had ceased. B, at the peak of the attack ventricular extrasystoles, bigeminy and short bursts of paroxysmal tachycardia appeared.

and exercise tests were within normal limits. (4) The attacks occurred at approximately the same time each twenty-four hours. (5) Each attack consisted of about forty rhythmically recurring bouts of pain. The attacks were remarkably cyclic in character. (6) The attacks were thought by some to be psychogenic in origin. (7) The electrocardiogram during pain showed marked ST elevation and reciprocal ST depression in standard leads. (8) The electrocardiogram was normal one to two minutes after the pain subsided. (9) Administration of nitroglycerin terminated the recurrent pains and their associated electrocardiographic abnormalities. (10) Six months after the onset, myocardial infarction occurred. (11) The infarction was located at the same site as the previous attacks of ischemia, as shown by ST segment elevation in the electrocardiogram. (12) There was a remarkable and immediate cessation of "rest-pain" after myocardial infarction. The reason for this loss of pain is probably that infarcted myocardium cannot give rise to pain. (Personally observed case, kindly referred by Alfred W. Kornbluth, M.D.)

CASE II. A forty-two year old engineer had episodes of severe substernal pain coming on at rest. The attacks occurred initially once or twice weekly and were never provoked by exertion. The patient believed, in fact, that exercise during the pain tended to relieve it. On Sundays he was accustomed to prolonged, heavy physical labor, but at no time did the pain occur during such work.

Over a thirteen-month period the pain gradually became more frequent and severe. Near the apex of severe attacks he noticed irregularity of his pulse. Later, as each attack reached a certain degree of severity, the arrhythmia appeared predictably and disappeared as the attacks waned. He found that reclining during the erratic action of his heart usually relieved the faintness. He felt faint during the arrhythmia but not during less severe pain without arrhythmia. One morning he was seized by an especially severe attack of pain associated with arrhythmia and faintness. As he arose from his chair to find a place to lie down, he fell to the floor and struck his head. He was unconscious for five to ten minutes, after which he was removed to the hospital for several weeks of study.

During his hospital stay he suffered daily attacks of anginal pain. The pain showed a definite and equal waxing and waning period. Attacks varied from a mild seizure of one to two minutes' duration to a severe seizure of twenty minutes' duration. He was especially likely to suffer pain at rest around 8:00 P.M., 4:00 A.M., and again on arising and walking to the bathroom in the morning. There was no pallor during attacks.

At the height of a severe attack the electrocardiogram showed ST elevation in leads II, III and aVF, and reciprocal depression in lead I. (Fig. 4A.) The R wave increased in height in the same leads that showed ST elevation. At the apex of the attack, ventricular extrasystoles, bigeminy and short runs of irregular paroxysmal ventricular tachycardia appeared. (Fig. 4B.) If an electrocardiogram was taken at the beginning of a severe attack, it was normal. During a *moderate* attack the ST segment was moderately elevated, but the QRS complex remained normal, and no arrhythmia appeared. (Fig. 5.) During *mild* attacks, there were only minor aberrations of the electrocardiogram and the T wave appeared spuriously improved. (Fig. 6.)

Blood pressure, pulse pressure and heart rate did not significantly change during the entire course of four different attacks. All laboratory studies were normal except for mildly elevated serum transaminase values on two occasions of 52 and 56 units. All other transaminase values were normal.

The patient had been a heavy cigarette smoker but five months after the onset of angina he stopped smoking. This did not affect the frequency of the attacks. An attempt to induce pain or electrocardiographic changes by smoking failed. An exercise test failed to provoke pain or the characteristic ST elevation. ST depression appeared instead.

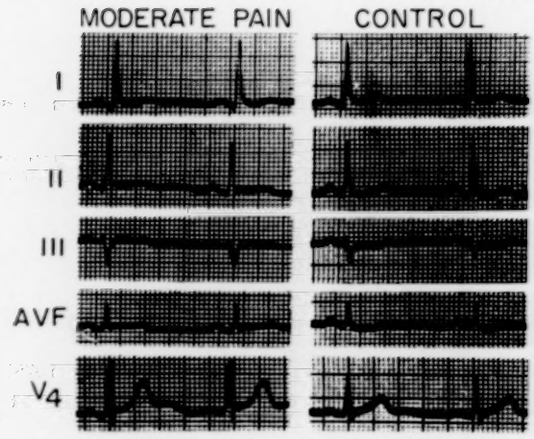


FIG. 5. Electrocardiogram during a moderate attack. Note the slight ST elevation in leads II, aVF and V_4. There were no QRS changes and no arrhythmias.

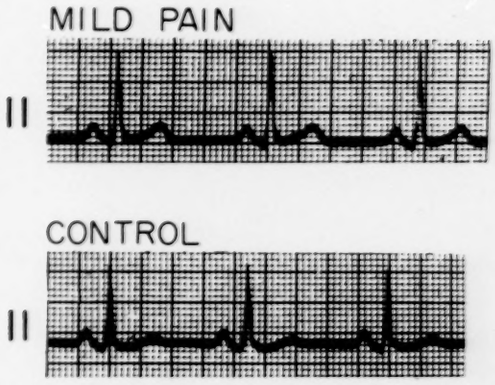


FIG. 6. Electrocardiogram during a mild attack. No significant electrocardiographic changes were seen. Note the spurious improvement of the T waves during attack. (Four other patients showed more striking improvement.)

Because of the strong probability that temporary increased tonus of a coronary artery is responsible for the attacks of this variant form of angina pectoris (see discussion under "Pathophysiology"), nylidrin hydrochloride (Arlidin®) was administered [*15*]. This agent induces vasodilation of sympathetic origin. It was given in doses of 6 to 24 mg., four to five times daily. Special efforts were made to administer the drug shortly before the anticipated time of attacks. The patient, who is an unusually accurate observer, reported an immediate and marked decrease in the severity of his attacks. Recently he has rarely required nitroglycerin (Fig. 7) and has experienced only rare episodes of pain during the past ten months.

Comments: This patient demonstrated the following salient features. (1) During the *severe* attacks he had ventricular arrhythmias which became increasingly alarming as the pain intensified. At the peak of pain, runs of ventricular tachycardia appeared. (2) Ventricular tachycardia was the likely cause of his syncope during attacks, and might represent a form of Adams-Stokes syndrome. (3) The R wave of his electrocardiogram became very high during *severe* attacks, probably due to local intraventricular block [*10,16,17*]. (4) The waxing and waning periods of the pain were about equal, while in angina pectoris the waxing period is ordinarily longer than the waning period. (5) During *moderate* attacks there was mild ST segment elevation (1 or 2 mm.). (6) During a *mild* attack or early in the course of a severe attack, the electrocardiogram was normal and neither arrhythmia nor QRS change appeared. Therefore a normal electrocardiogram obtained during a mild attack or early in the course of a more severe attack does not rule out the presence of the variant form of angina pectoris. (7) During a mild attack there was spurious improvement in this patient's electrocardiogram since the low T wave temporarily became taller. (Fig. 6.) (8) One of the theories advanced to explain the attacks is that there is a lowering of blood pressure, decrease in pulse pressure, or increase in heart rate. These vital signs remained unchanged during four attacks. (9) Occasional mild elevation of serum transaminase was probably a reflection of the intense myocardial ischemia (other patients had normal values). Since the electrocardiograms in each attack returned to normal within a few minutes after the pain stopped, there could scarcely have been any myocardial necrosis to account for this slight elevation. Furthermore, it has been amply shown that an elevated serum transaminase may be found in the absence of tissue necrosis. (10) An exercise test failed to evoke pain or ST elevation; ST depression appeared instead. (11) Smoking had no effect on the syndrome. (12) The administration of nylidrin hydrochloride (Arlidin), a drug which promotes vasodilation of sympathetic origin, appeared to prevent the attacks.

CASE III. A fifty-eight year old normotensive diabetic man suffered frequent episodes of angina at rest. At times he had to take as many as 30 nitroglycerin tablets a day. On three occasions in 1954 and 1955 electrocardiograms were obtained during spontaneous episodes of angina. These showed marked ST elevations of 8 mm. in lead II and 14 mm. in lead III, and reciprocal depression of 6 mm. in lead I. (Fig. 1B.) Within thirty minutes after the relief of the chest pain, the electrocardiogram always returned to its previous

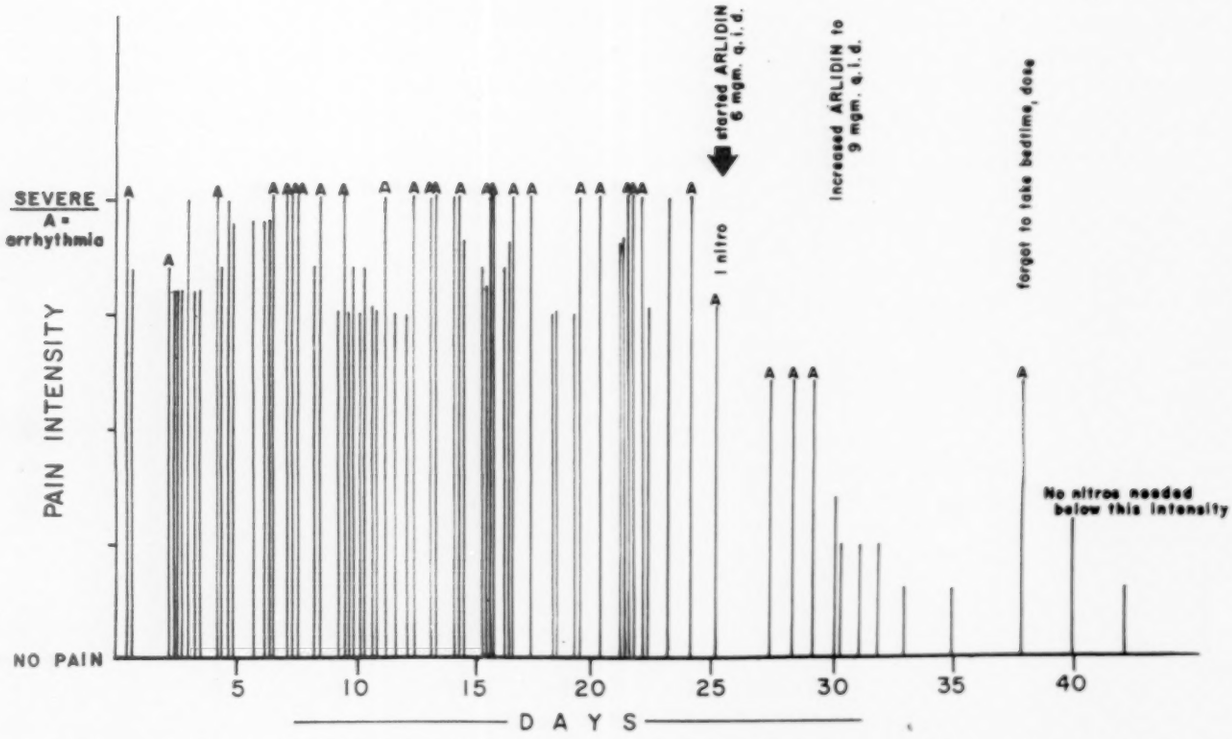


FIG. 7. Case II. Effect of nylidrin hydrochloride therapy on frequency and severity of attacks. After nylidrin hydrochloride was started both the frequency and severity of attacks greatly diminished. Some of the attacks were extremely mild; they seemed to abort themselves before reaching an intensity where nitroglycerin was needed. After thousands of attacks over a period of more than two years, this was the first time that such abortive attacks occurred. Innumerable pharmacologic agents had been tried on this patient without any effect whatsoever. The nitrites were the only drugs of value. The occurrence of ventricular arrhythmias at the peak of an attack is indicated by "A."

pattern. The exact duration of the changes is not known because electrocardiograms were not taken throughout the attacks. Serial tracings taken afterward showed no evidence of recent infarction. Because of the severity of the angina and congestive failure, the patient was given three courses of radioactive iodine in 1955, which resulted in mild relief of the angina but no improvement in the heart failure. His condition deteriorated and he suffered recurring episodes of anginal pain and chronic congestive failure. He died in May 1956.

At autopsy both major coronary arteries were found to be markedly sclerotic and there was an old anterior infarct. The large posterior coronary artery which supplied the area of the heart that had given rise to the ST elevation was approximately 80 per cent occluded, but the small lumen was not completely obstructed. (Fig. 8.)

Comments: (1) This patient suffered recurring episodes of pain at rest during which the electrocardiogram showed striking ST elevations in leads II and III, and ST depressions in lead I. These changes disappeared with cessation of pain. (2) Autopsy one and a half years later showed advanced sclerosis of the coronary arteries. Although a small lumen remained patent, the main posterior coronary artery was ap-

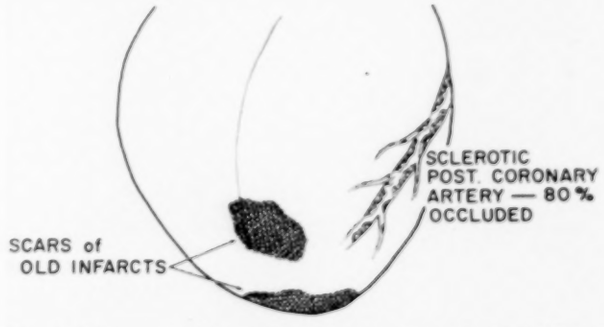


FIG. 8. Diagram of the autopsy findings in a patient (Case III) who had the variant form of angina pectoris. During attacks there was ST elevation in leads II, III and aVF (see Fig. 1B). At autopsy, the posterior coronary artery was 80 per cent occluded. Slight transient increase in tonus of this artery could cause complete obstruction and thus account for severe ischemia of the inferior and posterior portions of the heart during the attacks. This artery was a major source of blood supply to this portion of the heart. (Courtesy of M. J. GOLDMAN.)

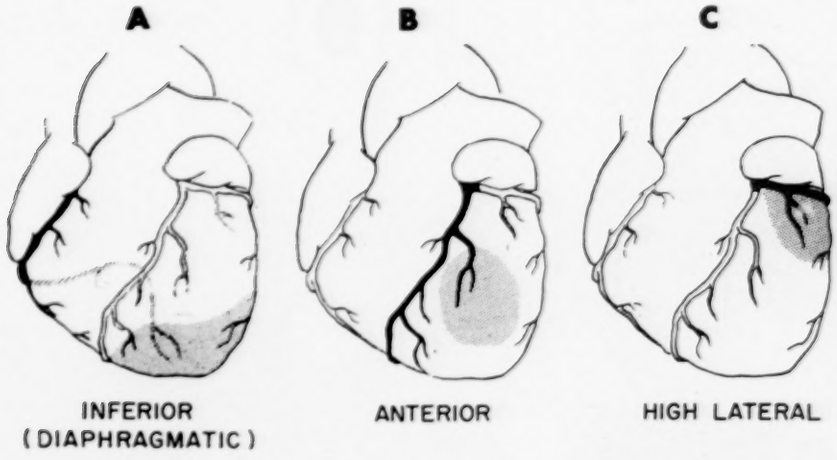


FIG. 9. Location of ischemic areas during episodes of pain in patients with the variant form. Note that these areas are supplied by the large coronary arteries. Subsequent infarction occurs in the same portion of the heart that became ischemic during attacks of pain. A, involvement of the posterior descending branch of the right coronary artery gives rise to ischemia in the posteroinferior portions (diaphragmatic) of the heart. B, involvement of the anterior descending coronary artery or one of its major branches gives rise to ischemia in the anterior portion of the heart. C, involvement of the left circumflex artery or one of its major branches gives rise to ischemia in the high lateral region of the heart. Other varieties have been found.

proximately 80 per cent occluded. (3) This artery most probably was the major source of the blood supply to the inferior and posterior portion of the myocardium, the area which gave rise to the ST elevations (leads II, III and aVF). A modest increase in tonus of a tiny portion of just one non-calcified site of this artery easily could have occluded the lumen and caused the attacks. Two other autopsies performed on patients who had the variant form of angina pectoris showed essentially the same pathological findings [*5,7*].

COMPARISON OF THE VARIANT AND THE CLASSIC FORM OF ANGINA PECTORIS

We have personally observed or inspected the hospital records of twenty cases of the variant form of angina pectoris, and in addition have found twelve cases described in the literature. The major characteristics of this type of angina are consistent. From a review of these thirty-two cases, the following differences and similarities have been noted.

(1) The pain of the variant form of angina pectoris occurs with the subject at rest or during ordinary activity. It is not brought on by exercise. It occurs *without increased cardiac work.* Classic angina pectoris occurs if the work of the heart is increased. (2) The location of the pain is identical with that of angina pectoris, but the duration generally is longer and the pain often more severe. (3) In some patients the pain is cyclic, with peaks of remarkable constancy every few minutes, forming a sine wave pattern. (4) Many patients describe attacks with distinct waxing and waning of equal duration, whereas in angina pectoris the waning period is shorter and more abrupt than the waxing period. (5) Pain often occurs at approximately the same time each day. (6) The administration of nitroglycerin promptly relieves both forms of angina. (7) The electrocardiogram during a severe attack of pain, without exception shows striking ST elevations with reciprocal depressions. The electrocardiograms may be unchanged at the beginning of a severe attack, or during a slight attack.* Spurious improvement may appear in a previously abnormal electrocardiogram. (8) The areas of the myocardium that give rise to ST elevation during attacks in every case correspond to the distribution of one large coronary artery and therefore to the known

* Rarely, during an attack of classic angina pectoris, a small area of ST segment elevation may appear on the electrocardiogram. This differs from the variant form in which the area of ST elevation is very extensive. The mechanism and experimental reproduction of this small ST segment elevation in angina pectoris will be dealt with in the forthcoming monograph.

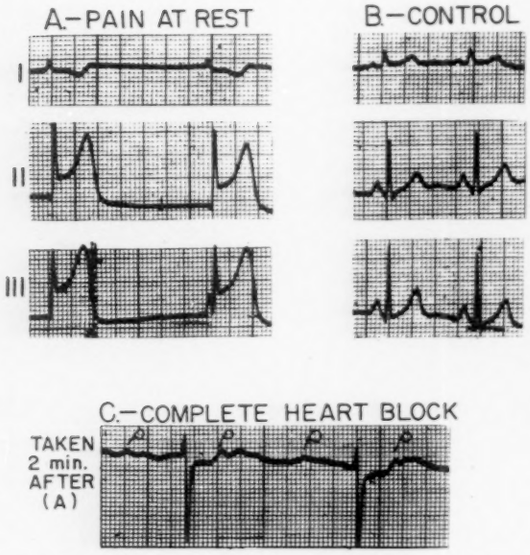


FIG. 10. Transient complete heart block with attacks of pain in the variant form of angina pectoris. A, electrocardiogram taken during attack of pain in patient at rest. There is marked ST elevation characteristic of the variant form in leads II and III, and reciprocal depression in lead I. Heart block is probably present. (Courtesy of A. EKMEKCI and Z. KAVURT.) B, electrocardiogram taken about an hour after the attack of pain. Tracing shows normal sinus rhythm and all symptoms had disappeared. C, transient complete heart block during pain. Ten minutes after (C), patient felt completely well, pain was gone, pulse rate normal.

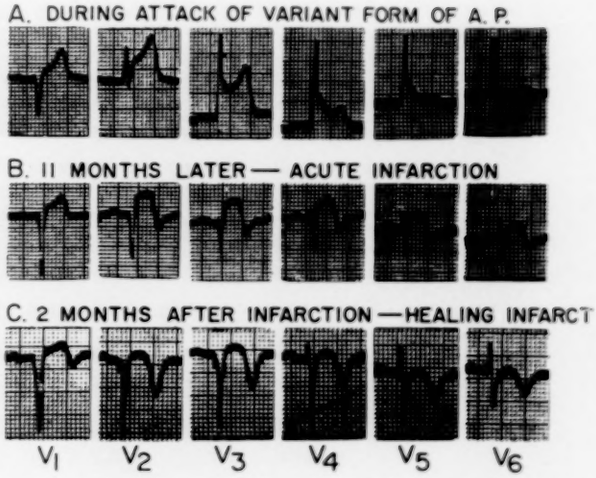


FIG. 11. Identical location of infarction and previous attacks of angina pectoris variant. Tracings of a fifty-seven year old man in whom an infarct developed in the same region that became ischemic during attacks of the variant form of angina pectoris. (Courtesy of M. J. GOLDMAN.) A, during an attack of pain, the electrocardiogram showed marked ST elevation in the V leads. B, An infarct developed eleven months later. Characteristic changes are in the same leads as in (A), indicating that infarction occurred in the same location as the ischemia during attack of pain. C, electrocardiogram shows healing infarct two months later.

locations of myocardial infarction; i.e., massive anterior, anteroseptal, inferior or diaphragmatic, antero-inferior, or high lateral. (Fig. 9.) (9) The QRS complex of the electrocardiogram is affected frequently during the severe attack.

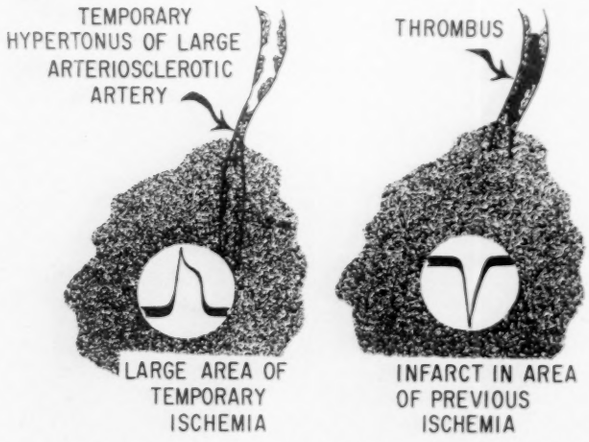


FIG. 12. Theory of location of infarction. If myocardial infarction occurs, the area involved is the same as that which became ischemic during previous attacks of pain. The location of possible future infarction can thus be predicted.

The R wave may become taller and broader (as in Case II), or even temporarily disappear [*13*]. (10) Arrhythmias, particularly ventricular, appear during the attack of the variant form much more frequently than during an attack of classic angina pectoris. About half the patients with the variant form have arrhythmias during the attack. One patient (Case II) had syncope as a result of ventricular tachycardia during an episode. Drs. A. Ekmekci and Z. Kavurt of Istanbul, Turkey, observed another patient in whom posterior myocardial ischemia led to transient heart block and faintness during attacks of the variant form of angina pectoris. (Fig. 10.) (11) Infarction, thus far, occurred in the same area of the heart that gave rise to the elevated ST segments during pain attacks in the variant form (twelve cases). (Figs. 11 and 12.) The location of the infarct, therefore, is predictable. This is not true in angina pectoris. (12) The exercise tolerance test failed to reproduce an attack in the variant form (6 cases). It may be normal or it may give rise to ST depressions. There is no pain during this ST depression. (Fig. 13.) (13) The two types of angina, classic and variant, involve different and distinct chemical disturbances [*27*]. (14) The

clinical diagnosis of angina pectoris usually is simple, owing to long acquaintance with the syndrome. The clinical diagnosis of the variant form requires careful study. (15) Acute emotional storms do not precipitate attacks of the variant form, but frequently cause attacks of angina pectoris. (16) The patient with the variant form of angina pectoris usually has greater distress than the patient with the classic form. The patient with classic angina can control and predict his pain to a considerable degree because of its relation to effort. The pain of the variant form, however, strikes without warning or apparent cause. (17) Preliminary observations in three of four patients suggest that the administration of nylidrin hydrochloride tends to prevent attacks of the variant form of angina pectoris. Because this compound increases cardiac output, it is said to be contraindicated in severe cases of classic angina pectoris. The use of other sympathomimetic vasodilator drugs may be carefully evaluated as they are developed. (18) Attacks of angina pectoris are due to a *diffuse* disturbance of the heart. This statement is based on the following observations: (a) It has been shown that in angina pectoris direct epicardial leads show multiple small islands of abnormality on all aspects of both ventricles [*28*]. In the variant form only *one* large area is physiologically disturbed. (Fig. 9.) (b) If myocardial infarction occurs in the variant form, the attacks of anginal pain, in our limited experience, are abolished immediately and completely (ten cases, one exception). This is not true of classic angina pectoris in which pain actually may become worse after myocardial infarction. In only rare cases of angina pectoris (uncomplicated by heart failure, auricular fibrillation or excessive rest) are patients relieved of pain after a myocardial infarction.

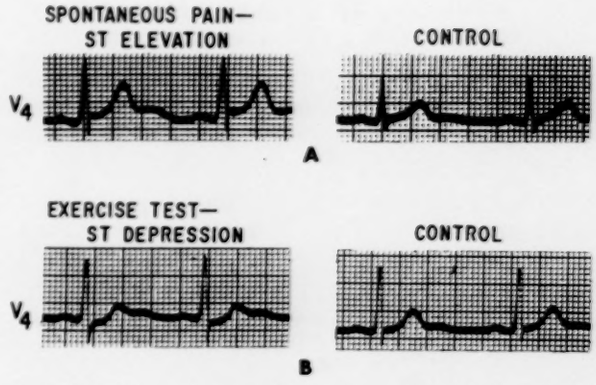


FIG. 13. Comparison of (A) spontaneous pain; and (B) exercise test (Master two-step) without pain. A, during spontaneous pain (moderate attack) there was the characteristic ST elevation. B, during the exercise test there was no pain and the ST segment was depressed in V_4, with less striking depression in leads I, II and III.

PATHOLOGY

Coronary atherosclerosis is common to both forms of angina pectoris. The pathological findings, however, bear no constant relationship to the syndrome of angina pectoris [*18*]. Patients with severe coronary atherosclerosis may not have anginal pain. Other patients with significantly less coronary artery disease may have severe anginal attacks. On this account an understanding of the relationship between coronary sclerosis and angina pectoris was historically delayed for many decades [*19–21*]. The same lack of fixed association probably is true of the variant form, although more autopsy data will be needed to clarify this. The finding of a large partially occluded coronary artery with a small but patent lumen is not limited to patients suffering from this form of angina but occurs also in patients who either have no symptoms, or who have the classic form of angina pectoris. The distinctive dissimilarities of the conditions are due to profound physiological and chemical [*27*] rather than anatomical differences.

PATHOPHYSIOLOGY

Myocardial infarction almost always is the result of coronary atherosclerosis. Since it occurs so commonly in the course of the variant form of angina pectoris, it can be assumed that coronary atherosclerosis is present here also. Moreover, since the infarction occurs in the same area of the heart that gave rise to the ST elevations during the spontaneous attacks, it is clear that atherosclerosis of a single large coronary vessel is the major pathology of both the angina and the later infarction. (Fig. 12.) This conclusion is strengthened by the fact that the area of myocardium giving rise to ST elevation during a spontaneous attack of the variant form of angina pectoris is the same as the areas classically involved by myocardial infarction. This does not imply, however, that in the variant form *only* a single large coronary artery is sclerotic. Undoubtedly other coronary vessels also are diseased, but in the typical case, these other arteries do not appear to play a significant role in producing the clinical picture.

It is suggested that the variant type of angina pectoris results from temporary occlusion of a large diseased artery with a narrow lumen due to a normal increase in tonus of the vessel wall. Spontaneous and cyclic changes in vascular tone can be readily seen in the central artery of the rabbits' ear and in other arteries.

The evidence that temporarily increased tonus precipitates the attack is as follows: (1) The attack characteristically occurs with the subject at rest, when hypertonic activity of the artery is physiologically greatest. It has been shown by observing arteries of mammals that temporary increases of vascular tone occur at rest and disappear with exertion or increased metabolism. (2) The attack is transient, and the electrocardiogram quickly reverts to normal. (3) The areas of the ST elevation during the anginal attacks are the same as those supplied by the major coronary arteries. (Fig. 9.) (4) Intermittent occlusion of a large coronary artery in a dog reproduces all the major clinical and electrocardiographic features of the attack. (See section on "Experimental Reproduction.") (5) The attack is promptly relieved by the administration of nitroglycerin, an agent which relieves arterial and arteriolar hypertonus. (6) The attack is not due to coronary insufficiency in its usual meaning, since causative disturbances which decrease coronary blood flow, such as paroxysmal tachycardia, fall in blood pressure, and the like, are lacking. (7) The pain often is cyclic in character, corresponding to the observed behavior of spontaneous recurring arterial hypertonus at rest. (8) In the three autopsy cases a tiny but still patent lumen has been observed in a large diseased coronary artery. Even a modest or normal degree of increased tone in such a vessel would lead to complete, although temporary, obstruction. (9) Transient complete heart block has been observed in one patient during attacks. It is hard to conceive of this resulting from any factor other than severe ischemia from a temporary interruption of blood flow to the conduction system of the heart. (Fig. 10.) (10) Preliminary observations suggest that the administration of nylidrin hydrochloride seems to prevent attacks. This compound induces vasodilation of sympathetic origin.

Others who have reported cases of anginal pain in patients at rest also have suggested spontaneous hypertonus as an explanation. Many have used the term "spasm."

EXPERIMENTAL REPRODUCTION

To test the foregoing explanation of the pathophysiology of the variant form of angina pectoris, the syndrome was reproduced in twenty-five dogs by intermittent occlusion of a large coronary artery. A tie was slipped loosely around a large coronary vessel. When the tie was tightened and the vessel occluded, an area of ischemia appeared, giving rise to the ST segment elevation in the corresponding electrocardiographic leads. This area became cyanotic; it lost its contractility and demonstrated systolic ballooning. ST depression was registered from the opposite side of the heart. The R wave often became taller and broader, and monophasic waves commonly occurred. Various arrhythmias often appeared. The arrhythmias most frequently were ventricular and consisted of extrasystoles, pulsus bigeminus and ventricular tachycardia. These disturbances in rhythm resembled those that appear in some patients during attacks of the variant form of angina pectoris. When the tie was loosened, the ST segment shift disappeared, the R wave became normal and the arrhythmias disappeared. These changes could be reproduced repeatedly by tightening or loosening the ligature. If the ligature was left too long, the animal died of ventricular fibrillation. The arrhythmic effects of coronary artery ligation have been observed repeatedly in the past. Moreover, lightly anesthetized animals show signs of suffering severe pain when the coronary artery is ligated [*22–23*]. The clinical and electrocardiographic aspects of the variant form of angina pectoris thus have been reproduced. The results strongly support the theory that intermittent occlusion of a diseased vessel by hypertonus is the cause of this syndrome. (Fig. 14.)

INCIDENCE

The incidence of this variant form of angina pectoris is unknown but the following appears valid from the limited number of cases studied. Although not nearly as common as angina pectoris, it is not a rare syndrome. It seems to be sufficiently frequent so that the cognizant physician will find cases in his practice. It shares with angina pectoris the same age distribution (average age forty to sixty years), and is more common in men than women. Professional men including physicians seem to be especially affected.

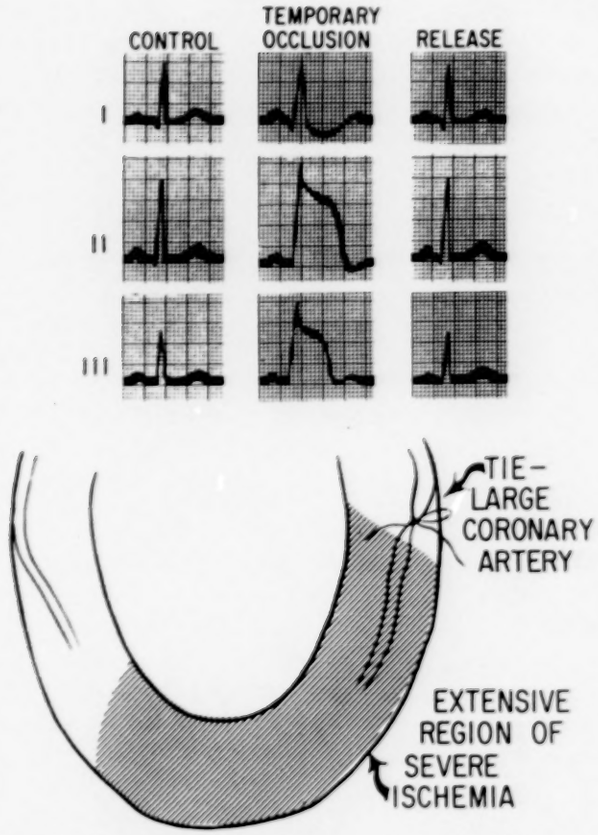


FIG. 14. Experimental production of the variant form of angina pectoris. Temporary occlusion of a large coronary artery in dogs reproduces the clinical syndrome: (1) ST elevations appear over the ischemic area, with reciprocal ST depressions; (2) QRS changes often appear; (3) ventricular arrhythmias are frequent; (4) the electrocardiographic changes disappear rapidly after the obstruction is relieved; (5) if the obstruction remains too long, death often ensues from ventricular fibrillation; (6) if a small artery is tied, the variant form of angina pectoris does not occur; (7) severe pain results when the coronary artery is obstructed (this experiment has been performed by others on unanesthetized dogs).

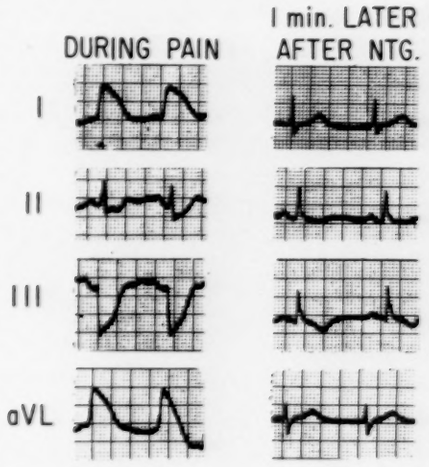


FIG. 15. Spontaneous disappearance of attacks. A sixty-two year old diabetic physician with a six months' history of mild angina pectoris (classic type). The angina changed character, occurring predominantly at rest and often awakening him from sleep. Climbing two flights of stairs no longer caused chest pain. Over a period of months the variant form of angina gradually improved, then almost disappeared. Infarction did not occur. (Courtesy of DR. C. S. STEIN, JR.) Note the monophasic waves and QRS changes. In some patients attacks gradually disappear, probably due to the development of a collateral circulation from less diseased vessels.

COURSE

The variant form of angina pectoris may follow a variety of courses during its natural development. Death may occur during an attack, probably from ventricular fibrillation (two cases), or from myocardial infarction; should the patient recover from the infarction, the angina characteristically disappears immediately. Progressive coronary artery disease may develop with all of its attendant disabilities (Case III). The attacks may gradually disappear, probably as better collateral circulation develops (at least three cases). (Fig. 15.) It is not uncommon for both the variant and classic forms of angina pectoris to occur together in the same patient. The variant form may appear before, after, or at about the same time, as the classic form. After myocardial infarction the variant form of angina pectoris disappears, but in some patients it may be later replaced by the classic form of angina.

DIAGNOSIS

Clinical Diagnosis. The key to the diagnosis of the variant form of angina pectoris, much as the classic form, is the taking of a painstaking history. The more information the patient gives, the greater the diagnostic certainty. Charting the time, severity and circumstances of the attacks is helpful. The significant and characteristic points are: the cyclic nature of the pain; its occurrence at rest; the waxing and waning periods of equal length; the arrhythmia at the apex of the attack; the recurrence at approximately the same time each twenty-four hours; the failure of excitement to induce the attack; and the occasional relief by exertion.

The effect of nitroglycerin therapy distinguishes the variant and classic forms of angina pectoris from many other cardiac and non-cardiac syndromes. The patient should be

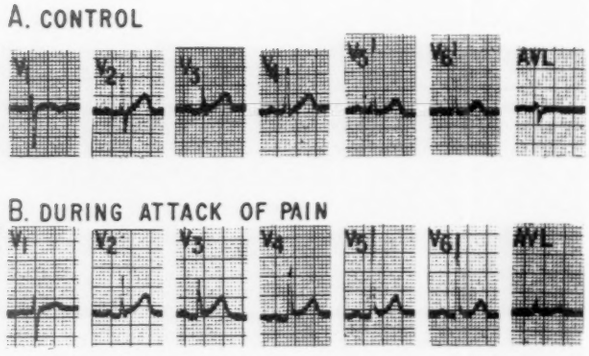


FIG. 16. Clinical diagnosis. A, a definite clinical diagnosis of the variant form of angina pectoris was made because of typical history and effect of nitrites. The electrocardiogram was normal. B, three weeks after the clinical diagnosis, an electrocardiogram was obtained during a mild attack with pain down both arms. Note the ST elevation and the spurious improvement in aVL.

given sufficient nitroglycerin o cause a mild throbbing headache. He should be instructed to observe carefully the time between taking the tablet and relief, and the relationship between relief and the headache. He should not, of course, be told what to expect. In the variant form of angina pectoris the pain disappears about a minute after taking nitroglycerin and the relief is concomitant usually with the onset of the throbbing headache.

The clinical diagnosis can be confirmed by subsequent electrocardiograms during attacks. (Fig. 16.) Electrocardiographic confirmation is not always necessary.

Electrocardiographic Diagnosis. Electrocardiographic corroboration is much more difficult than in classic angina pectoris, since the attacks cannot be induced but must be awaited. It is essential that two electrocardiograms be taken on each patient, one during pain and the other immediately after. Hospitalization often is required so that electrocardiograms may be taken promptly whenever pain occurs. The demonstration of the impressive ST segment elevation and its complete disappearance after a relatively short time clearly identifies the variant syndrome. If the first tracing only is taken, acute myocardial infarction invariably is diagnosed (a mistake we have made in the past). This error will be further reinforced should a slight transaminase elevation be found, such as was intermittently present in Case II. A normal electrocardiogram obtained during a mild attack or early in the course of a severe one does not rule out the presence of the variant form of angina pectoris. The patient must be instructed not to take nitroglycerin, and the electrocardiogram should be obtained as near the apex of a severe attack as possible. An electrocardiogram showing "improvement" should be studied carefully for this may be the only graphic change in the variant form.

The exercise test fails to provoke pain or the characteristic ST elevation in the variant form of angina pectoris; either there is no ST deviation or ST depression appears. (Fig. 13.) Significant ST depression after exercise also occurs in the classic form of angina pectoris and in some patients with asymptomatic coronary artery diseases, suggesting in this point alone a disturbed response of unknown nature to increased cardiac work common to all three conditions. In our experience, exercise tests were of little value in the diagnosis of the variant form of angina pectoris.

DIFFERENTIAL DIAGNOSIS

Anginal pain in a subject at rest may be an ominous sign. Its differential diagnosis, therefore, is vitally important. The following four cardiac syndromes, among others, should be differentiated from the variant form of angina pectoris: (1) *Myocardial infarction:* This may produce anginal-type chest pain in subjects at rest. (2) *Angina pectoris:* Episodes of pain may occur at rest in some patients. The differential points have been summarized. (3) *Pre-infarction angina:* This differs from the variant form of angina pectoris as follows: (a) Pre-infarction angina, by definition, leads to infarction in a relatively short time. The variant form may continue for years without infarction. (b) The attacks of pre-infarction angina tend to grow increasingly more severe. The attacks of the variant form generally preserve the same character or may gradually improve. (c) The electrocardiogram taken during episodes of pre-infarction angina is normal or shows ST depression, in contradistinction to the elevated ST segment of the variant form. (d) The administration of nitroglycerin is effective in the variant form of angina pectoris but has a variable effect in pre-infarction angina. (4) *Coronary insufficiency:* (a) Attacks of "coronary insufficiency" ordinarily occur as a result of a precipitating factor that reduces coronary artery blood flow, such as hemorrhage, hypotension, prolonged rapid arrhythmias, pulmonary embolism, and the like. Such precipitating factors are absent in the variant form of angina pectoris.

(b) The electrocardiogram during an attack of coronary insufficiency is either normal or shows ST depression instead of ST segment elevation.

There are many other causes of cardiac pain in the subject at rest (such as dissecting aneurysm, aortic insufficiency of rheumatic origin, pericarditis, left-sided heart failure or some patients with Cheyne-Stokes respiration). These enter into the differential diagnosis to a lesser extent, and are not considered here. Chest pain in a subject at rest, of course, may not be of cardiac origin.

SUGGESTED TREATMENT

Anticoagulants should be used in the hope of preventing subsequent infarction. Nitroglycerin is especially important, and can be life-saving. The longer acting nitrites may be of prophylactic benefit. The use of antiarrhythmic drugs are indicated in patients in whom arrhythmias develop during attacks.

Conservative treatment for atherosclerosis should be considered (weight reduction, low fat, low cholesterol, low caloric diet, carefully observed exercises and avoidance of cigarette smoking). On general principles it is advisable to have the patient stop smoking or reduce to moderation.

Preliminary observations on a limited number of patients suggest that administration of nylidrin hydrochloride may prevent the attacks. This drug promotes sympathetic vasodilatation. It is given in doses of 6 to 12 mg. several times daily. In one case it was necessary gradually to increase the dosage to 250 mg. during twenty-four hours. Since many patients can predict the time of their attacks, it is possible to prevent the attack by giving a dose of the drug shortly before this time. The use of nylidrin hydrochloride is said to be contraindicated in severe Heberden's angina for it tends to increase the cardiac output and thus may precipitate attacks.

A "sit-up" bed or gradual elevation of the head of the bed may be useful in patients who have predominately nocturnal attacks.

Since the coronary artery that is involved and the cause of the attacks may be recognized from the electrocardiogram, the May, Bailey or Cannon [*24–26*] surgical procedures, in which the lumen of an atheromatous coronary artery is enlarged, might be considered in selected cases as a last resort. The production of hypothyroidism had no dramatic effect in one case. Sympathectomy has not been tried. We have had no experience with the operations proposed by Beck and Vineberg.

SUMMARY AND CONCLUSIONS

A variant form of angina pectoris is described. This syndrome differs from classic angina pectoris in several respects.

The pain is not brought on by increased cardiac work, is usually more severe and of longer duration, often waxes and wanes in cyclic fashion, often occurs at about the same time each day, and is not relieved by rest. Arrhythmias, often ventricular, occur in about 50 per cent of cases during the peak of the pain. The pain usually disappears immediately after infarction.

The variant form of angina exhibits the following electrocardiographic features which are in contrast to those found in the classic form of angina pectoris: (1) The ST segments are elevated transiently and often considerably during an attack, although there may be no ST changes with a mild attack or at the onset of a severe attack. (2) Reciprocal ST depression occurs in standard leads. (3) ST and T wave changes during an attack occasionally may seem to improve a previously abnormal electrocardiogram. (4) Areas of myocardium giving rise to ST elevation correspond to the distribution of a large coronary artery. (5) The area of myocardium giving rise to ST segment elevation during anginal pain often is the site of future infarction. (6) Exercise does not produce ST elevation. (7) The R wave may become taller and broader during an attack.

The clinical diagnosis of the variant form of angina is possible in typical cases even without the use of the electrocardiogram.

Temporary increased tonus of a large narrowed coronary artery is suggested as the cause of attacks of pain in the variant form of angina. Chemical changes in the myocardium differ from those occurring in classic angina pectoris [*27*].

Preliminary observations suggest that attacks may be prevented by the administration of nilidrin hydrochloride. Anticoagulants appear to be indicated in the treatment of the variant form of angina.

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J. J. Sampson, L. Schwartz, E. Shapiro and D. Sodi-Pallares.

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Paroxysmal Nocturnal Hemoglobinuria*

I. Clinical Studies

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IMPAIRED acetylcholinesterase activity has been noted in the red cells of patients with paroxysmal nocturnal hemoglobinuria [*1–3*]. A detailed description of this phenomenon in six patients with paroxysmal nocturnal hemoglobinuria (PNH) is presented in the companion article [*4*]. The purpose of the present communication is to provide the clinical protocols necessary to ascertain the diagnosis of PNH and to note some unusual or little recognized features.

METHODS FOR SPECIAL TESTS

Ham and Crosby Tests. The Ham test for acid hemolysis was performed by a modification of the recent descriptions by Ham [*5*] and Wintrobe [*6*]. The Crosby test, in which hemolysis is brought about or accentuated by the addition of thrombin, was performed after the manner described by its originator [*7*]. Thrombin† of bovine origin was used.

"Heat Sensitivity" Test. This screening test was performed according to the method of Hegglin and Maier [*8*]. Although these authors termed this procedure the "heat-resistance" test, we prefer the term "heat sensitivity" since the latter property is characteristic of the PNH red cell.

Plasma Hemoglobin. The biochemical quantitation of hemoglobin in plasma or serum was carried out by Crosby and Furth's modification [*9*] of the original Bing and Baker benzidine method [*10*]. The benzidine reagent was further purified by the method of Bing [*11*].

The procedures involved in collecting the blood and processing the plasma were performed with great care in an attempt to keep technical hemolysis to an absolute minimum. Saftidonor sets‡ were used for the collection of the blood [*12*]. Native (without anticoagulant) platelet-free plasma was processed by previously described methods, with reliance on the use of low temperatures and silicone-treated equipment [*13*]. Red cells (and other formed elements) were quickly and meticulously removed by high-speed centrifugation to avoid technical disruption of the red cells *in vitro*. With this method the plasma hemoglobin concentrations in normal subjects were less than 1.0 mg. per 100 ml. Usually the concentration was less than 0.5 mg. per 100 ml., and occasionally no hemoglobin was detectable.

Urine Hemoglobin. The same reagents were employed as in the plasma hemoglobin test. Only qualitative results were determined.

Urine Hemosiderin. The method used was as described by Wintrobe [*6*].

Donath-Landsteiner Test. The test for cold hemolysins was modified after that described by Wintrobe [*6*].

CASE REPORTS

CASE 1. A thirty-three year old Negro gardener was first admitted in January 1947. He had been hospitalized as a serviceman in 1944 in India because of the onset of anemia and dark urine which initially was attributed to malaria. Following failure to respond to antimalarial therapy as well as to multiple transfusions, liver and iron, he was transferred to an army hospital in the United States, and subsequently discharged from the service with a diagnosis of hemolytic anemia of unknown type. Weakness and anemia persisted, and the patient required periodic transfusions. Six weeks prior to admission bilateral pretibial ulcers developed. Past and family histories were non-contributory.

The patient was of small stature (63 inches, 135 pounds) but of normal bony framework. The mucous membranes appeared pale and the scleras slightly icteric. In the right eye there were patches of thin sclera revealing large areas of dull, slate-blue choroid. (Fig. 1.) Funduscopic examination showed no abnormalities. Examination of the heart revealed a soft, grade 2 apical systolic murmur. The blood pres-

† Thrombin (bovine) was obtained through the courtesy of Parke, Davis and Co., Detroit, Michigan.

‡ Saftidonor sets were kindly provided by Dr. E. B. McQuarrie, Biochemical Research Division, Cutter Laboratories, Berkeley, California.

* From the Hematology Service, Department of Medicine, Vanderbilt University School of Medicine and Hospital, Nashville, Tennessee. This study was supported by Research Grant H-3509 from the Division of Research Grants and Fellowships of the National Institutes of Health, the John A. Hartford Foundation, Inc., New York, New York, and the Brownlee O. Currey Memorial Fund.



FIG. 1. Case I. Patches of slate blue sclera in the right eye of the patient. This appearance was attributed to abnormally thin sclera revealing the color of the underlying choroid.

sure was 120/70 mm. Hg. The liver and spleen were not palpable. Bilateral cryptorchidism was present. There were large bilateral pretibial ulcers, but no varicosities or other evidence of large vessel disease were evident in the extremities. Neurological examination revealed normal findings. (Other family members were not available for examination for blue scleras or cryptorchidism. By the rather sketchy history available, such anomalies were not present.)

Blood counts on admission were as follows: volume of packed red cells 13 per cent, red cells 1.77 million per cu. mm., hemoglobin 4.5 gm. per 100 ml., reticulocytes 20 per cent, and white cells 4,000 per cu. mm. Detailed laboratory studies are summarized in the Laboratory Studies section and in Table I. Such studies established the diagnosis of PNH.

The pretibial ulcers gradually healed with residual scarring (Fig. 2) over a period of four months of use of penicillin ointment and iontophoresis with mecholyl bromide. All attempts at transfusion were accompanied by severe febrile reactions and exacerbations of hemoglobinuria.

From 1946 through March 1958, the patient was readmitted on eight occasions. Preceding each admission there was an exacerbation or increase in the severity of weakness and the episodes of hemoglobinuria. A therapeutic trial of alkali failed to abolish the hemoglobinuria. The patient was treated intermittently with oral preparations of iron from 1946 to 1958.



FIG. 2. Case I. Scars of healed pretibial ulcers. The ulcers developed in November 1946. Photograph was taken in 1957.

The patient's blood group was B. Originally his blood was typed as Rh positive, and he received such blood. When the correct blood type was finally ascertained as Rh negative in 1948, the serum contained a titer of 1:128 of anti-Rh_o antibodies. The indirect Coombs' test was positive, the direct test was negative. From 1947 to February 1958, the patient refused further transfusions. During this time the volume of packed red cells varied from 24 to 33 per cent. In February 1958, he received two transfusions of compatible whole blood elsewhere without known reaction.

In February 1957, the patient had attacks of vertigo, right temporal headaches, blurred vision and pares-

TABLE I

HEMATOLOGIC DATA IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Data	Case I	Case II	Case III	Case IV	Case V	Case VI
Age at onset of disease (yr.); race; sex	30, N ♂	31, N ♂	39, W ♂	54, W ♂	38, W ♂	38, N ♀
Year of onset of disease	1944	1951	1956	1955	1957	1950
Years covered by present report	1947–1958	1952–1958	1956–1958	1957–1958	1957–1958	1957–1958
Volume of packed red cells (%)*	24–33†	21–33†	5–24	21–27	21–31	14–29
Reticulocytes (%)*	5.8–20	2.3–26	3.2–12	7.7–20.6	8.1–15.5	4.3–38
White cells (per cu. mm.)	2,600–6,200	4,000–8,200	2,200–5,900	2,200–7,000	1,700–4,000	5,000–10,900
Differential white cell count:						
Segmented neutrophils (%)	36–70	44–74	22–56	45–68	61–78	41–91
Lymphocytes (%)	28–48	22–52	44–73	18–38	11–26	5.5–34
Platelets (per cu. mm.)	40,000–90,000	115,000–176,000	11,000–96,000	23,000–87,000	94,000–150,000	189,000–337,000
Plasma hemoglobin (mg. per 100 ml.)	22	80	22	28–130	32	18–28
Blood group and type	B-negative	B-negative	A-negative	A-positive	O-positive	O-positive

* These are the values on admission or pretransfusion.

† These two patients refused transfusions during the period of observation.

thesias of the left arm and leg, culminating in temporary paralysis of these extremities. The blood pressure was 148/70 mm. Hg. Recovery was rapid and several weeks later neurological examination was normal except for slight weakness in the left arm and leg. A spinal fluid examination, roentgenograms of the skull and an electroencephalogram were interpreted as being normal. There was no evidence of hemorrhagic diathesis; laboratory tests of hemostatic function were normal.

The most recent admission was in February 1958 for low back and periumbilical pain, marked jaundice and massive ascites of three weeks' duration. The liver was palpable 5 cm. below the right costal margin, and the tip of the spleen could be felt. Laboratory studies revealed: volume of packed red cells 34 per cent, white cell count 4,300 per cu. mm., reticulocytes 3 per cent, fecal urobilinogen concentrations 116 and 480 Ehrlich units per 100 gm. on two occasions, and absence of occult blood in stools. Results of liver function tests were: cephalin flocculation 4 plus, serum alkaline phosphatase 25 King-Armstrong units, serum total protein 9.4 gm. per cent, albumin 4.3 gm. per cent, globulin 5.1 gm. per cent, serum total bilirubin 10.1 (3.2 direct), prothrombin activity 50 per cent of normal, and serum transaminase 260 units per ml. Serum electrophoresis showed a marked increase in the proportion of gamma globulin ("broad band"). An esophagogram revealed "minimal esophageal varices." A long history of excessive alcoholism was strongly suspected but could not be definitely ascertained. The patient improved clinically on supportive therapy but biochemical evidence of hepatocellular damage persisted. He was given a month's leave of absence from which he failed to return.

Case II. A twenty-eight year old Negro farmer was first admitted in June 1948 because of an infected thorn injury of the left little finger. He had experienced a brief attack of jaundice at age five without subsequent recurrence. There was a past history of treated syphilis. The family history was non-contributory. Urinalysis and blood counts were normal. The infection responded to penicillin therapy.

The patient was readmitted in March 1952 with a one-year history of progressive weakness and anemia and episodes of syncope and blurred vision. There had also been attacks of pain in the muscles and joints accompanied by the voiding of dark urine in the morning with subsequent clearing during the day.

The patient was a well developed, obese, dark-skinned male. The weight was 170 pounds and the height 69 inches. Pertinent physical findings included pallor of the mucous membranes and nailbeds and slight scleral icterus. Firm, enlarged lymph nodes (2 to 3 cm. in diameter) were present in the left cervical and supraclavicular regions. Funduscopic examination revealed no abnormalities. There was a grade 3 blowing systolic murmur heard best in the pulmonic region. The blood pressure was 110/60 mm. Hg. The liver and spleen were not palpable. Neurological examination was within normal limits.

Blood counts on admission revealed: volume of packed red cells 21 per cent, hemoglobin 7.0 gm. per 100 ml., reticulocytes 15 per cent, and white cells 4,000 per cu. mm. Detailed laboratory studies established the diagnosis of PNH (see Laboratory Studies section and Table 1).

The hemoglobinuria, fever and malaise disappeared within a week. A biopsy specimen of a left posterior cervical node revealed tuberculous adenitis. Roentgenograms of the chest and skull as well as electroencephalograms were normal. The seizures were attributed to "hyperventilation." The patient refused blood transfusions. The volume of packed red cells has since varied from 24 to 33 per cent. On discharge, treatment with an oral preparation of iron was prescribed, but it is doubtful if the patient ever took this medication faithfully.

He was readmitted in November 1952 for a trial of dicumarol therapy. Adequate suppression of prothrombin activity was obtained, but there was no significant hematological response. After one month therapy was finally discontinued because of an episode of right-sided renal colic and gross hematuria. Intravenous pyelograms showed only "minimal blunting of the calyces." Studies directed toward the possibility of renal infectious or inflammatory disease were within normal limits.

The patient has continued to experience weakness and episodes of syncope, low back pain and hemoglobinuria. He has never returned to work, and remains in fair condition on a program of limited activity. Examination of blood smears during two separate admissions in 1957 revealed the additional feature of hypochromia. Red cell indices were MCV 80 cubic microns, MCH 20 micromicrograms, MCHC 25 gm. per 100 ml. packed red cells. On these last two admissions the serum iron concentrations were 43 and 55 γ per cent, respectively, the residual iron-binding capacities 385 and 400 γ per cent, and the iron saturation 10 and 12 per cent.* These studies suggest the additional feature of iron deficiency.

Case III. A thirty-nine year old white farmer was first admitted in December 1956 complaining of weakness and fatigue of one month's duration. Three weeks prior to admission he had had edema of the face and ankles, dyspnea on exertion, and dark urine, most prominent in the morning specimens and clearing greatly during the day. His associates noted that he appeared "yellow." Four days prior to admission his family physician discovered that his hemoglobin was 4 gm. per 100 ml. The past and family histories were non-contributory. There was a history of repeated exposure to fertilizers (nitrates, phosphates and

* These determinations were kindly performed by Dr. Calvin W. Woodruff of the Department of Pediatrics.

potash) and to Paris Green and DDT sprays but no known reaction to these compounds.

The patient was a well developed and nourished white man. He weighed 152 pounds and was 68 inches tall. Marked pallor and mild icterus were present. There were mild, bilateral contractures of the fifth fingers which had been present since birth. (Members of the family were not available for examination but by history no contractures of the fingers were present.) Funduscopic examination revealed a "few splinter hemorrhages and small exudates" but no papilledema. The lungs were clear to percussion and auscultation. A loud grade 3 systolic murmur was heard over the entire precordium. The blood pressure was 118/78 mm. Hg. The liver and spleen were not palpable. There was 3-plus pitting edema of the ankles. Neurological examination was within normal limits.

Initial blood counts were as follows: volume of packed red cells 13 per cent, hemoglobin 4.7 gm. per 100 ml., red cells 1.1 million per cu. mm., reticulocytes 7.2 per cent, white cells 4,100 per cu. mm. and platelets 11,000 per cu. mm. Bone marrow aspiration smears were very hypocellular. Two surgical marrow biopsy specimens were obtained, one from each iliac crest, on separate occasions. The sections showed severe hypoplasia with occasional islands of active hematopoiesis. A diagnosis of aplastic anemia was made, and the patient was given 8 units of whole blood, without reaction and with temporary elevation of the volume of packed red cells to normal. He became asymptomatic, the edema of the ankles and cardiac murmur disappeared, and the retinal hemorrhages slowly resolved. A four-week course of prednisone produced no clear-cut effects. Only after the screening "heat sensitivity" test was found to be positive was the history suggestive of hemoglobinuria properly assessed. Definitive studies (shown herein) then established the diagnosis of PNH. Thereafter, only washed red cells were used for transfusions. The first two units elevated the hematocrit from 21 per cent to 30 per cent, and the next two units to 40 per cent.

The patient has been readmitted six times, at approximate intervals of two months. On five of the six admissions the volume of packed red cells has varied from 14 to 24 per cent. On the average, 4 to 6 units of washed red cells have sufficed to elevate the volume of packed red cells to 37 to 42 per cent. On each admission he has complained of weakness, dyspnea and episodes of intermittent hemoglobinuria. In October 1957 he had an extensive bulbar subconjunctival hemorrhage in the left eye. The systolic murmur and edema of the ankles have repeatedly disappeared following transfusions of washed red cells.

The admission in February 1958 is of particular interest since the patient had postponed his return from the customary two months interval to five months, and the volume of packed red cells had fallen to 5.5 per cent. Symptoms of weakness, dyspnea, edema of the ankles and hemoglobinuria had been present for two weeks. The blood pressure was 110/50 mm. Hg and the pulse 100. Bilateral papilledema was noted, as were many fresh retinal hemorrhages, numerous petechiae on the trunk and extremities, and many fine rales at the base of the right lung. In addition to the systolic murmur usually present during episodes of severe anemia, a grade 2 diastolic murmur was heard in the fourth left intercostal space and a protodiastolic gallop rhythm at the apex. The liver was palpable 4 cm. below the right costal margin; the spleen could not be felt. There was 1-plus edema of the ankles.

The hemoglobin concentration was 2.0 gm. per 100 ml. Other blood counts revealed: white cells 4,100 per cu. mm., reticulocytes 7.8 per cent, and platelets 28,000 per cu. mm. The serum total bilirubin was 0.9 mg. per cent (0.1 mg. per cent direct). The plasma prothrombic activity was 27 per cent of normal. Results of other liver function tests obtained within forty-eight hours after admission were normal. (The volume of packed red cells had been raised to 7 to 13 per cent by red cell transfusions by the time the liver function tests were obtained.) Several stool specimens were negative for occult blood. The urine showed no hemoglobin on two occasions. Bleeding and clotting times were normal. The tourniquet test was strongly positive. The circulation time was nine seconds. The chest roentgenogram and electrocardiogram were within normal limits.

Shortly after admission the patient went into circulatory collapse, the systolic blood pressure falling to 80 mm. Hg. He was given digoxin and a unit of *packed* red cells (not washed) to which he had a febrile reaction (102°F.) but no apparent hemoglobinuria. During the next few days he was given 5 units of washed red cells without reaction, and the volume of packed red cells rose to 40 per cent. As the volume of packed red cells rose, the papilledema, petechiae, hepatomegaly, cardiac murmurs, gallop rhythm and hypoprothrombinemia disappeared. The retinal hemorrhages underwent slow resolution. The patient became asymptomatic and was discharged. His subsequent admissions at intervals of two months for correction of the recurring anemia by transfusions of washed red cells have been essentially uncomplicated.

CASE IV. A fifty-six year old white farmer was admitted in February 1957 complaining of weakness of several months' duration. For two years he had experienced episodes of voiding dark urine ("Coca Cola" in appearance). These attacks occurred at intervals of one to three months and lasted two to three days. The dark color was particularly obvious in the first morning specimen. The attacks were preceded by malaise and cramps in the thighs and calves, and were followed by weakness.

Five months prior to admission he had several painful bullae containing red fluid on the right thigh

and one such bulla over the right internal malleolus. These lesions were approximately 2 cm. in diameter and elevated 1 cm. Subsequently they regressed, leaving superficial flat scars. The past and family histories were non-contributory.

The patient was a well developed and nourished white man. The weight was 156 pounds and the height 70 inches. Pallor and mild jaundice were present. There were a cluster of five round, superficial scars on the upper anterior right thigh (Fig. 3) and a single, similar lesion over the right internal malleolus. (Biopsy specimen of one of the lesions on the thigh revealed only subcutaneous fibrosis.) Funduscopic examination was within normal limits. There was a soft blowing apical systolic murmur. Otherwise, on examination, the heart and lungs were normal. The blood pressure was 134/70 mm. Hg. The liver was not palpable, but the tip of the spleen could be felt during deep inspiration. The neurological examination disclosed no abnormalities.

The patient had active hemoglobinuria on admission. The initial blood counts were: volume of packed red cells 23 per cent, hemoglobin 7.3 gm. per 100 ml., red cells 1.9 million per cu. mm., white cells 3,100 per cu. mm., reticulocytes 8.4 per cent, and platelets 60,000 per cu. mm. Detailed studies (to be described) established the diagnosis of PNH.

The hemoglobinuria cleared in four to five days. The patient was transfused with 2 units of washed red cells which elevated the hematocrit to 36 per cent. He became asymptomatic, and the cardiac murmur disappeared.

The patient has been readmitted on four occasions for transfusions or study. He continues to have intermittent weakness and episodes of hemoglobinuria, with leg cramps and mild jaundice, at intervals of one to three weeks. The episodes of hemoglobinuria last two to four days. He has received 2 to 4 units of washed red cells at intervals of one to four months. Pretransfusion hematocrits have ranged from 21 to 27 per cent. Two units of washed cells suffice to elevate the hematocrit by 6 to 11 percentage points, and 4 units by 14 to 21 percentage points. There have been no reactions to the washed red cells. The transfusions have increased the patient's sense of well-being sufficiently to permit him to return to light farm duties following each set of transfusions.

Case v. A thirty-eight year old white stockroom clerk was admitted in June 1957 with a history of episodic passage of dark urine, of four months' duration. The attacks occurred every one to two weeks and persisted for about three days. The urine was "dark as Coca Cola" on arising in the morning but subsequently cleared greatly during the day. Ten weeks before admission he had consulted his family physician because of the onset of weakness and jaundice. The red and white cell counts were both said to be low. The past and family histories were non-contributory.

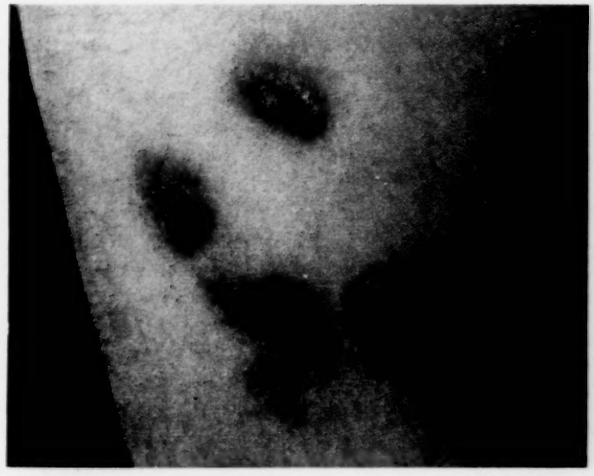


Fig. 3. Case iv. Scars of healed "hemorrhagic bullae" (?) on right thigh of patient. A similar, single lesion was present over the right internal malleolus.

The patient was a well developed and nourished white man. The weight was 152 pounds and the height 69 inches. Pallor and mild icterus were present. Funduscopic examination revealed no abnormalities. Examination of the heart and lungs was within normal limits. The blood pressure was 120/80 mm. Hg. The liver and spleen were not palpable. Rectal examination revealed a small polyp. Neurological examination was within normal limits.

Blood counts on admission revealed the following: volume of packed red cells 31.7 per cent, hemoglobin 9.8 gm. per 100 ml., red cells 2.86 million per cu. mm., reticulocytes 8.1 per cent, white cells 4,000 per cu. mm., and platelets 133,000 per cu. mm. Special studies (to be described) established the diagnosis of PNH. Hemoglobinuria was present on admission but disappeared within five days. Infusion of 2 units of washed red cells increased the volume of packed red cells to 40.8 per cent. The patient was discharged improved on June 26, 1957, with instructions to his family physician for periodic transfusions of washed red cells.

He was readmitted in February 1958 because of increasing weakness and jaundice. Washed red cells had been given on one occasion in November 1957. He had worked for only six weeks after discharge. Intermittent hemoglobinuria had persisted. The packed red cell volume was 21 per cent. Four units of washed red cells elevated the value to 40 per cent.

Following discharge a program of rehabilitation was attempted. The patient has returned every month for outpatient checkup and transfusion of 1 or 2 units of washed red cells. By this means the volume of packed red cells has been kept above 31 per cent, and the patient has felt strong enough to continue work. There have been no reactions to transfused washed red cells. On at least three occasions hemoglobinuria of one to two weeks' duration ceased

following multiple transfusions of washed red cells given on the same day. This clearing did not begin immediately after the completion of the transfusions but started with the first specimen of the following morning and persisted for at least one week on each occasion.

CASE VI. A forty-five year old Negro female domestic was first admitted in April 1957 for investigation of an anemia. In the summer of 1950 she had experienced weakness and the voiding of dark urine for several weeks. In June 1951 she was hospitalized elsewhere for anemia associated with the voiding of dark urine ("dark as Coca Cola"), jaundice, weakness, syncope and palpitations. Eight units of whole blood were administered with good response and without apparent reaction. Thereafter the patient became asymptomatic. She was followed up by her family physician who treated her intermittently with the administration of liver, vitamins and iron. Periodically she was noted to be anemic and mildly jaundiced but remained generally asymptomatic until February 1957 when she again experienced weakness, jaundice and the voiding of dark urine. The urine cleared in about one week but because of persistent weakness the patient was referred to Vanderbilt University Hospital for further study. The past and family histories were non-contributory.

The patient was a very light-skinned Negro with many Caucasian facial features. The weight was 130 pounds and the height 64 inches. There was a light brownish discoloration over the forehead and cheeks. Pallor of the mucous membranes and scleral icterus were present. Funduscopic examination revealed no abnormalities. There was a grade 2 systolic murmur heard over the entire precordium. Otherwise the examination of the heart and lungs was within normal limits. The blood pressure was 130/80 mm. Hg. The liver and spleen were not palpable. Pelvic and neurological examinations were normal.

Blood counts on admission showed the following values: volume of packed red cells 21 per cent, hemoglobin 7.8 gm. per 100 ml., red cells 2.0 million per cu. mm., reticulocytes 18.1 per cent, white cells 5,500 per cu. mm., and platelets 233,000 per cu. mm. L.E. cell tests were repeatedly negative. The half-life of radiochromium-tagged red cells was eight days (lower limit of normal, twenty-six days). Results of the "heat sensitivity" and urinary hemosiderin tests were strongly positive, and a diagnosis of PNH was suspected. However, reactions to the Ham and Crosby tests were negative on two occasions. The patient experienced no hemoglobinuria during this admission. Two transfusions with compatible whole blood resulted in febrile transfusion reactions and no increase in volume of packed red cells. Two units of packed red cells were administered without reaction and with a rise in the volume of packed red cells to 34.5 per cent.

From May 1957 until readmission in July 1958 the patient was followed up in the outpatient department. She was treated with two courses of hydrocortisone, one for two months and the other for four months, with doses varying from 20 to 60 mg. per day. Neither course of therapy increased the volume of packed red cells. In the one instance an upper respiratory infection developed within several days after steroid therapy was discontinued, and the hematocrit fell within one week from 26 to 14 per cent, without evidence of hemoglobinuria. During the second course of steroid therapy the hematocrit remained stable at 31 to 33 per cent for six weeks but fell thereafter despite continuance of therapy.

The patient received thirteen transfusions during this fourteen-month period. Transfusions of whole blood, compatible by albumin and indirect Coombs' test crossmatch, led to severe febrile transfusion reactions with no elevation of the hematocrit. Packed red cells gave only mild reactions, and the use of washed red cells abolished the reactions and increased the hematocrit effectively. Mild to moderate icterus was intermittently present. The only time that the patient voided dark urine ("dark as Coca Cola") was while enroute on a trip to Texas. Results of the "heat sensitivity" test were repeatedly positive, but the Ham and Crosby tests were again negative.

Since the acetylcholinesterase activity of erythrocytes was found to be low in the five well established cases of PNH already discussed [*3*], the test was carried out in the present patient. On three occasions the acetylcholinesterase activity of her cells was found to be low [*4*]. The patient therefore was readmitted for further study. This time the results of the Ham test were definitely and repeatedly positive, but the Crosby test was again negative.

LABORATORY STUDIES

For convenience the laboratory studies in all six patients will be considered together.

Diagnostic Tests for Paroxysmal Nocturnal Hemoglobinuria. Hemoglobinuria: In patients I to V there was a history of hemoglobinuria ("urine dark as Coca Cola") and laboratory verification of this phenomenon on several occasions. Patient VI had only four known episodes of passage of dark urine, three prior to coming to Vanderbilt Hospital and one episode enroute on a trip to Texas; consequently no hemoglobinuric specimen was obtained from this patient. In all patients the nocturnal character was ascertained either by history or by direct observation of a morning urine specimen showing the most marked hemoglobinuria, with tendency to clearing in successive specimens during the day.

Hemoglobinemia: In all patients the plasma appeared grossly hemoglobinemic on multiple occasions. Elevated plasma hemoglobin concentrations were demonstrated in all patients tested as shown in

Table I. Methemalbumin was demonstrated spectroscopically in the plasma of patient IV.

Hemosiderinuria: In all cases the Prussian blue reaction repeatedly demonstrated large amounts of hemosiderin in urinary sediments, both in renal epithelial cells and extracellularly. Results of the test were so strongly positive that the supernatant test reagents were also dark blue in color.

"Heat sensitivity" test: This test was performed repeatedly in all cases and the results were strongly positive in each instance.

Ham and Crosby tests: In Cases I to V the results of these tests were positive on each of many occasions. In Case VI they were negative on two occasions in 1957 and on one occasion in early 1958. In July 1958 results of the Ham test were positive but the Crosby test was again negative.

General Hematological Studies. Volume of packed red cells: The range of admission or pretransfusion values for each patient is shown in Table I. The values for patients I and II were not influenced by previous transfusions since patient II had never received blood, and patient I refused further transfusions during most of the period covered by our records (1947–1958).

Reticulocytes: The range of admission or pretransfusion reticulocytes is shown in Table I.

Red cell indices and morphology: In all patients red cell indices were usually normocytic-normochromic to moderately macrocytic. The mean corpuscular volume, with rare exceptions, varied from 88 to 123 cubic microns. The blood smears consistently revealed slight to moderate anisocytosis, poikilocytosis, polychromatophilia and macrocytosis, and on occasion 1 or 2 nucleated red cells per 100 white cells. In Case IV slight stippling was noted in some blood smears. In Case VI marked polychromatophilia and stippling and moderate numbers of target cells were present. No spherocytes were seen in the smears of any patient. In Case II the patient had the additional feature of hypochromia and other evidence suggestive of iron deficiency (see Case Report).

White cells: The total leukocyte counts and the proportions of segmented neutrophils and of lymphocytes are shown in Table I. Five of the six patients had leukopenia (<5,000 cells per cu. mm.) at some time. In Case V leukopenia was constant. In Cases III and IV leukopenia was present on most occasions, but only in Case III was relative lymphocytosis a fairly regular accompaniment of leukopenia. In Cases IV and V, despite the leukopenia, relative lymphocytosis was not seen. In other respects the differential white cell counts were within normal limits.

Alkaline phosphatase stain of leukocytes: In Cases III to VI "buffy coat" blood smears were stained for alkaline phosphatase by the method of Gomori modified by Brodell and Swisher [*14*]. There was a marked reduction in alkaline phosphatase staining in all four, in agreement with the biochemical determinations of Beck and Valentine [*15*].

Platelets: The ranges of platelet counts are shown in Table I. Three of the six patients consistently had counts less than 100,000 per cu. mm.

Marrow studies: All the patients but one (Case III) had very cellular marrow aspiration smears. In Cases I and II the smears had been interpreted as showing "increased erythropoiesis" but were no longer available for further examination. In Cases IV to VI the proportion of normoblasts in the marrow smears were 75.8 per cent, 56 per cent and 41.8 per cent, respectively. In Cases V and VI megakaryocytes appeared adequate in number, and in Case IV somewhat reduced in number (the platelet count on the day of the marrow aspiration was 52,000 per cu. mm.).

In Case III, marrow aspiration smears revealed extreme hypocellularity. In January 1957 the marrow biopsy specimens showed marked hypoplasia with a few islands of intense hematopoiesis. In February 1958 marrow aspiration smears were very hypocellular with occasional small clumps of marrow.

Serum bilirubin: Serum bilirubin concentrations varied greatly in each patient, being normal on occasion. However, in all patients a value between 1.6 and 3.7 mg. per 100 ml. was attained at some time. The indirect-reacting bilirubin predominated.

Fecal urobilinogen: Fecal urobilinogen was determined in multiple random specimens. In all patients values exceeding 700 Ehrlich units per 100 gm. were obtained in some instances, even at times remote from transfusions.

Fragility of red cells: The osmotic fragility of fresh red cells was repeatedly found to be normal in all patients. In Cases IV, V and VI the osmotic fragility of red cells previously incubated at 37°C. for twenty-four hours was also normal. In Case IV the mechanical fragility was 2.5 per cent (normal < 5 per cent).

Coombs' tests: One patient (Case I) had a positive indirect Coombs' test, presumably as a result of Rh isosensitization from incompatible transfusions. The direct Coombs' test was negative. In all other patients results of both direct and indirect Coombs' tests were repeatedly negative. In Cases IV, V and VI detailed studies for erythrocytic antibodies were negative.*

Sickle cell tests: Results of sickle cell tests employing 2 per cent sodium metabisulfite solution were repeatedly negative in the three Negro patients (Cases I, II and VI) and in the one white patient tested (Case III). In these four patients hemoglobin electrophoresis revealed a normal pattern.

Donath-Landsteiner test: Results of the Donath-Landsteiner tests were negative in all six patients.

Hemostatic function tests: In Case III the patient had a clotting time of forty minutes (normal twenty to thirty minutes) on one occasion. In Cases III and IV the bleeding times ranged from three to eighteen minutes. In Case IV there have been no hemorrhagic difficulties.

* These determinations were kindly performed by Mr. W. H. Moore of the Immunohematology Laboratory, Vanderbilt University Hospital.

The tourniquet test has remained positive in Case III. At the time of severe anemia (hematocrit 5.5 per cent), this patient had temporarily diminished prothrombic activity. With these exceptions results of hemostatic function tests have otherwise been normal in the group of PNH patients.

Miscellaneous Laboratory Studies. Serological tests for syphilis: Results of serological tests for syphilis were repeatedly negative in all six patients.

Urinalysis and renal function tests: The heat and acetic acid tests for protein were positive during episodes of hemoglobinuria. Otherwise, routine urinalyses were, in general, normal in all patients. The specific gravity of at least one randomly collected urine specimen which was free of hemoglobin exceeded 1.020 in all patients. Phenolsulfonphthalein excretion was normal in 1957 and 1958 in the five patients tested (Cases I, III to VI). In all patients blood non-protein nitrogen values were repeatedly normal. Tests for urinary bile were within normal limits. The urinary urobilinogen was increased at some time in all patients. Urinary porphyrins were absent in the three patients tested (Cases III, IV and VI).

L.E. cell tests: Results of L.E. cell tests employing the roller tube method of Zinkham and Conley [*16*] were negative in the patients tested (Cases III to VI). No erythrophagocytosis was seen.

Liver function tests: The following tests were employed: serum bilirubin, cephalin flocculation, thymol turbidity, bromsulfonphthalein excretion, serum total protein, albumin and globulin, prothrombin time and alkaline phosphatase activity. The serum bilirubin concentrations and the prothrombin times have been previously discussed. In general, the biochemical tests for liver function were normal. A notable exception concerns the admission of one patient (Case I) in February 1958 at which time obvious and marked hepatocellular damage was an additional development.

The cephalin flocculation tests showed marked variation. In Case I the test has always been plus 3 to plus 4. In Cases II and III the cephalin flocculation test was plus 2 to plus 3 initially and repeatedly negative thereafter. In Cases IV and V the cephalin flocculation test was negative on the first admissions and plus 3 to plus 4 thereafter. In Case VI this test has been repeatedly negative. There was no over-all correlation between the degree of anemia or the number of transfusions given and the results of the cephalin flocculation tests.

Clinical radiologic studies: Chest roentgenograms were repeatedly normal in all cases except for evidence of moderate, diffuse emphysematous changes in Case IV. Cholecystograms were normal in all patients tested (Cases I, IV and V) except that at the time of marked hepatocellular damage in February 1958 there was no visualization of the gallbladder in Case I. Upper gastrointestinal series were negative in all the patients studied (Cases I, III to VI).

The bone roentgenograms appeared to be within normal limits in all cases. Complete bone surveys were performed in Cases I, II and III with negative results. An intravenous pyelogram was normal in Case I, and showed only "minimal blunting of the calyces" in Case II (see Case Report).

Electrocardiograms: Electrocardiograms showed no significant abnormality in any patient even at the time of severe anemia.

Somatic Body Type Study. It has been stated that patients with PNH exhibit a tendency to the "hypermorphic" ("ectomorphic") body type (legs long in proportion to body height; low sitting height; slender arms and legs; slender body; narrow nose, shoulders, thorax and hips) [*17*]. By gross inspection none of our PNH patients seemed to fit into this group. For somatotyping purposes Sheldon's method employing the ratio "height $\sqrt[3]{\text{weight}}$" was used [*18*]. The *minimum* ratio necessary for the slightest degree of preponderance of hypermorphism over other body types for the age of the patient was obtained from the tables of Sheldon and his associates [*18*]. The following are the values for Cases I to VI, respectively: 12.25 ($\geq$13.00), 12.45 ($\geq$12.95), 12.75 ($\geq$13.00), 12.85 ($\geq$12.85), 13.05 ($\geq$13.00) and 12.60 ($\geq$12.95). The first figure given represents the calculated ratio for the patient, and the figure in parenthesis the *minimum* value for hypermorphic tendency. The standards used were those for white men. Unfortunately, to our knowledge no detailed data are available for Negroes (Cases I, II and VI) or for women (Case VI). The calculated ratios for Cases I, II and VI were considerably below minimum values for hypermorphic tendency. Therefore, the standards for male and female Negroes would have to be startlingly different from that of white males for Cases I, II and VI to fall within the hypermorphic group.

Patients III to VI were recently available for reexamination. In all four, height equalled arm span within a tolerance of 2 cm. Sitting height-total height ratios exceeded 0.510. Mean values for American Negroes have been reported as 0.514 for males and 0.518 for females [*19*], but we were unable to locate mean values for white males. None of the patients had a distinctly aquiline nose. Neither were the fingers abnormally long or hyperextensible. In our opinion none of the six patients fulfill sufficient criteria to be placed in the hypermorphic group. None of the male patients (Cases I to V) had a female distribution of body hair in contrast to what has been noted in certain other cases [*17*].

COMMENTS

The protocols of the six patients provide sufficient evidence to establish the diagnosis of PNH. The clinical courses fit the pattern of this disorder, and the findings of hemoglobinuria,

hemoglobinemia, marked hemosiderinuria and positive Ham and Crosby tests are diagnostic.

Case VI deserves special comment. Since the result of the Ham test was initially negative, it is tempting to suggest that the finding of decreased erythrocyte acetylcholinesterase activity is the more sensitive test for PNH [*4*]. However, the possibility of error in the earlier Ham tests in this one instance cannot be excluded. Evidence that the negative results with the Crosby test in this patient were not due to technical error is provided by the fact that the same bovine thrombin was used which gave a positive test with the cells of another patient (Case IV). At present this finding remains unexplained.

The fact that three of our six patients are Negroes is of particular interest. Although Crosby in his outstanding review of PNH refers to Negro patients [*17*], the occurrence of this disorder in the Negro is not commonly appreciated. While one patient (Case VI) was a light-skinned Negro woman with obvious, considerable admixture of Caucasian blood, two patients (Cases I and II) were dark-skinned Negroes with negroid facies. Nevertheless, it is impossible to exclude Caucasian admixture in the American Negro [*19*]. It has been suggested that PNH patients tend to be of the "hypermorphic" body type [*17*]. Our patients did not fit rigid criteria for this category (*vide supra*).

At present no evidence exists that PNH is an heritable disorder [*17*]. This disease is not known to occur in family members. Dameshek has reported PNH in one of identical twins, the other of whom remained normal [*20*]. Our companion article revealed normal erythrocyte acetylcholinesterase activity in the members of the one family studied [*4*].

In Case I the patient has patches of slate-blue sclera in the right eye and also cryptorchidism, findings suggestive of congenital or developmental defects. Blue scleras are seen in osteogenesis imperfecta tarda, but other stigmas of this disorder such as bone changes and deafness were not present in Case I. McKusick suggested that blue scleras may occur as an isolated anomaly [*21*]. The absence of detectable family history for this defect in Case I and the presence of patchy, unilateral lesions rather than diffuse involvement suggest an isolated developmental defect rather than a truly heritable anomaly. In Case III the patient had bilateral fifth finger contractures (Dupuytren's contractures). While this may be an heritable anomaly [*21*], it was not present by history in other members of the family.

Pretibial ulcers are rare in PNH [*17*]. Larrain and his associates described the occurrence of a single ulcer on the ankle in a forty-one year old Chilean woman [*22*]. The ulcer on the ankle followed by several months the occurrence of severe, bilateral puerperal thrombophlebitis which in turn had antedated the diagnosis of PNH by one year. Perkins and his associates documented the case of a forty-nine year old white sailor with PNH, chronic alcoholism, peripheral neuritis, multiple thromboses of the superficial veins of all extremities, and the scars of many healed pretibial ulcers [*23*]. In Case I, a Negro man, the pretibial ulcers were not accompanied by any known predisposing factors or obvious large vessel disease. No sickle hemoglobin was detected. Perhaps the pretibial ulcers were associated with the alleged greater tendency of the Negro to develop such with any hemolytic disorder. This patient also had an episode suggestive of cerebral infarction. This episode and the pretibial ulcers may be common expressions of the thrombotic tendency ascribed to PNH [*17*]. Whether the cutaneous lesions of the thigh and ankle in Case IV, a white man, were also the result of small thrombi is likewise a matter of speculation. No other explanation was elicited.

Despite the frequency of thrombocytopenia, hemorrhagic complications are rare in PNH [*17*]. Only in Case III were there any hemorrhagic difficulties. These consisted of complications which could equally well be attributed to "pure" vascular abnormalities as to platelet deficiency *per se*, e.g., subconjunctival bulbar hemorrhage, retinal hemorrhages and petechiae.

Hepatocellular damage has not been singled out as a sequela of PNH. The occurrence of liver disease in Case I was thought to be an extraneous feature secondary to chronic alcoholism. By contrast, one patient (Case III) had no abnormality of biochemical liver function tests, even during the episode of profound anemia (volume of packed red cells 5.5 per cent), with the possible exception of deficient prothrombin activity. The variability of the results of the cephalin flocculation tests (from 0 to 4 plus) from patient to patient and from time to time in the same patient remains unexplained.

Renal impairment is not considered to be a part of the basic disorder in PNH [*17*]. Care must be taken to reserve final evaluation of

urinalysis and renal function for periods free of hemoglobinuria. Otherwise, misinterpretations will be made such as attributing the positive tests for urine protein to renal damage when actually the proteinuria may be due to the temporary presence of hemoglobin. Urinalyses and clinical tests of renal function remained normal in all our patients during intervals free of hemoglobinuria.

The markedly hypoplastic bone marrow in Case III illustrates the fact that impaired hematopoiesis occurs in PNH [*17*]. Commonly this is only functionally detectable, but morphologic marrow hypoplasia may also occur. In Case III the history suggesting hemoglobinuria and the finding of reticulocytosis were not initially appreciated. The policy of performing the simple screening "heat sensitivity" test in patients with a diagnosis of aplastic anemia, particularly when some degree of reticulocytosis is present, compensated for these oversights. It is significant that this patient with severely hypoplastic marrow has the greatest transfusion requirement of all six patients.

In our patients there was no uniformity in the white blood cell and platelet patterns. (Table I.) There were rather wide ranges in fluctuation of the leukocyte counts and to a lesser extent the platelet counts. There was no tendency to progressive deficiency of these formed elements over the years of observation. Indeed, leukopenia and thrombocytopenia were usually present at some time during the first hospitalizations. There was no over-all correlation between red and white cell and platelet concentrations except that the patient with hypoplastic marrow (Case III) had, in general, the greatest deficiencies of all of these formed elements.

Despite the frequency of leukopenia there was no increased incidence of severe or overwhelming infections, even in the patients treated with steroid drugs. Only one patient (Case III, with hypoplastic marrow) had relative lymphocytosis as a fairly regular accompaniment of leukopenia. The usual picture in the other five patients was the presence of a normal proportion of mature neutrophils in the differential count irrespective of whether the total leukocyte count was normal or low. It is possible that this finding and the absence of extreme leukopenia on most occasions may explain the fact that our patients have not experienced severe or overwhelming infections, such as were noted in other cases [*17*].

In none of our patients, even those treated with steroid drugs, did clinical or radiologic evidence of peptic ulceration develop, in contrast to the high incidence cited for this complication [*17*]. Nevertheless, in view of the potentially serious side-reactions to steroids, and their generally equivocal influence on the course of PNH, their use should ordinarily be reserved for special circumstances, such as a complicating autoimmune hemolytic process [*24*]. In none of our patients did a complicating autoimmune process develop.

Depletion of normal iron deposits due to increased renal excretion of iron was noted in some early case reports of PNH, i.e., before the ready availability of blood for transfusions [*17*]. Nowadays the iron loads provided by multiple transfusions probably compensate for the renal loss. In fact transfusion hemosiderosis may be present [*17*]. In Case II evidence of iron deficiency developed by the sixth year of disease. Although dietary sources of iron were considered adequate, there were probably no other exogenous sources since the patient steadfastly refused transfusions and most likely did not take the oral preparation of iron prescribed. By contrast, in Case IV a two-year period without extradietary sources of exogenous iron did not lead to evidence of iron deficiency. These data suggest that when it rarely occurs, a long period of time is required for iron deficiency to develop in PNH. Blood loss could conceivably have played a role in the development of iron deficiency in Case II. There was an episode of hematuria during dicumarol therapy. Nevertheless, it is our opinion that there was insufficient blood loss to play a significant role in this patient.

For eleven years one patient (Case I) refused transfusions, yet evidence of iron deficiency did not develop. Renal loss of iron may have been compensated for by the many transfusions received prior to 1947 and by more or less continuous therapy with an oral preparation of iron since.

Both the necessity and efficiency of a carefully planned program of rehabilitation based on periodic outpatient transfusions of washed red cells were confirmed in our patients [*25*]. Two patients (Cases I and II) were not rehabilitated, probably due in part to refusal to accept transfusions and in part to the security of pensions. One patient (Case III) belongs in a special category. Probably due in large measure to the

added feature of morphologically hypoplastic marrow, his transfusion requirements are so much greater than the others as to preclude satisfactory rehabilitation. Three patients (Cases IV, V and VI) have been regularly returned to their (relatively sedentary) activities and occupations. The precise level to which the volume of packed red cells should be brought periodically will vary from patient to patient. One patient (Case IV), a fifty-six year old farmer, with moderate emphysema probably requires periodic elevation of the hematocrit to about 35 per cent. Another patient (Case V), a thirty-nine year old stockroom clerk, does well with a lesser periodic elevation of the hematocrit. Another patient (Case VI), a forty-six year old Negro domestic, works regularly without noticeable difficulty as long as the packed cell volume is at least 25 per cent.

SUMMARY

The clinical and laboratory findings in six patients with paroxysmal nocturnal hemoglobinuria are presented.

Some unusual or little recognized features are discussed. These include occurrence of paroxysmal nocturnal hemoglobinuria in the Negro, presence of leg ulcers and skin lesions, hemorrhagic complications, and the development of iron deficiency.

In accord with previous suggestions of others, a carefully planned program of rehabilitation is advocated, based on periodic outpatient transfusions of washed red cells.

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ADDENDUM

One patient (Case I) died elsewhere in July 1958. Information regarding the terminal phase of the illness was scanty but compatible with death due to Laennec's cirrhosis. Postmortem examination was not performed.

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Paroxysmal Nocturnal Hemoglobinuria*

II. Erythrocyte Acetylcholinesterase Defect

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THERE is general agreement that the basic abnormality in paroxysmal nocturnal hemoglobinuria (PNH) resides in the red cell and not in the plasma. PNH red cells are hemolyzed *in vitro* both by the patient's own serum and by normal serum. Normal red cells infused into a patient with PNH have a normal survival time. Furthermore, when the infused normal cells are separated even weeks later from an aliquot of recipient's blood, they do not undergo lysis *in vitro* as do PNH cells [*1*].

The precise nature of the PNH erythrocyte defect remains unsettled but is thought to reside in the stromal fabric [*2*]. Rodbard was the first to suggest that the erythrocytes in this disorder have an abnormal lipid surface structure [*3*]. Harris, Prankerd and Westerman demonstrated differences in the phospholipid content of normal and PNH red cells [*4*]. The phosphorylcholine content was reduced in five of six samples of PNH cells, and the phosphorylserine increased in four of six samples. The PNH cells also contained increased amounts of lipid nitrogen and cholesterol. More recently Munn and Crosby provided additional evidence of abnormality in the lipid pattern of stromal lipoprotein [*5*].

The rate of entry of radioactive phosphorus has been reported to be markedly reduced in PNH erythrocytes [*6,7*]. In addition Altman, Tabechian and Young demonstrated a decreased rate of efflux of radioactive phosphorus [*7*]. Hellem and Skaug also noted an increased turnover of the labile phosphate of adenosine triphosphate (ATP) [*6*], and Prankerd found no defect in the phosphorylation of adenosine diphosphate (ADP) in PNH cells [*8*].

Matthes, Schubothe and Lindemann reported that electron microscopy demonstrated the presence in PNH of a patchy, pitted erythrocytic surface with many clefts [*9*]. This finding has been both confirmed [*10,11*] and denied [*12*].

Reduced erythrocyte acetylcholinesterase (AChE) activity in four patients with PNH has been reported (in abstract form) from our laboratory [*13*]. The present communication documents this finding in detail in a total of eight patients with PNH.

MATERIALS AND METHODS

Patient Material. The patients are designated as Cases I to VI, to correspond with the clinical reports in the companion article [*14*]. Dr. Carl F. Hinz, Jr., of the Western Reserve University School of Medicine kindly provided specimens of red cells from two other patients with PNH. The Western Reserve patients will be designated Cases VII and VIII. Unless otherwise indicated the erythrocyte enzyme studies reported refer to specimens obtained at times remote from transfusions. In Case I the specimens were obtained thirty days after transfusion of 2 units of whole blood. In Case II the patient had never received a transfusion. The other patients had not received a transfusion for periods of two to five months prior to the time of the current studies.

Preparation of Packed Red Cell Specimens. Blood was collected from an antecubital vein into silicone-treated tubes containing a small amount of heparin† (0.5 mg. per 10 ml. blood). The blood was then centrifuged at high speed (10,000 times gravity) for ten minutes to pack the red cells. Following meticulous removal of all the plasma possible, packed red cell samples were removed by aspiration in several ways. Some specimens were removed in a random manner so as to be representative of cells at all depths of the column. These specimens will be designated "whole packed

† Heparin sodium, 1,000 U.S.P. units (10 mg.) per ml., was kindly supplied by The Upjohn Company, Kalamazoo, Michigan.

* From the Hematology Service, Department of Medicine, Vanderbilt University School of Medicine and Hospital, Nashville, Tennessee. This study was supported by Research Grant H-3509 from the Division of Research Grants and Grant 2A-5129 from the Division of Arthritis and Metabolic Diseases, National Institutes of Health and by the John A. Hartford Foundation, Inc., New York, New York.

cells." In other aliquots the very top (reticulocyte-rich) and bottom (reticulocyte-poor) layers were removed separately by careful aspiration. These will be designated "top layer packed cells" and "bottom layer packed cells," respectively.

The packed cell specimens were then washed three times with large volumes of 0.85 per cent sodium chloride solution and finally packed again by centrifugation at 3,000 r.p.m. for five minutes. The enzyme activity of 0.2 ml. portions of the washed packed cells was determined. The reticulocyte percentage in whole blood was taken as the value for the whole packed cell specimens. To obtain reticulocyte percentages in the top and bottom packed cells it was necessary to dilute small aliquots in the original plasma. Saline suspensions of the packed red cells proved unsatisfactory for reticulocyte counts.

In most instances the enzyme assays were carried out immediately after preparation of the packed cell specimens. In some cases the specimens were stored at 4° for twenty-four hours prior to enzyme assays. Such storage did not appear to influence the results obtained. The washed packed red cell specimens in Cases VII and VIII were prepared by Dr. Carl Hinz. A specimen of normal packed cells was simultaneously prepared. The three specimens were stored at 4° and airmailed in a refrigerated container. The enzyme determinations were carried out immediately after arrival, i.e., about twelve hours after shipment.

Preparation of Erythrocyte Stroma. Red cell stroma was prepared by a modification of Howe's method [*15*]. Three milliliters of washed packed erythrocytes were lysed by the addition of 30 ml. of distilled water, and 4.1 ml. of 0.154 M acetate buffer (pH 4.45) were then added. The final pH of this mixture was 5.6. Following chilling in crushed ice for fifteen minutes, the erythrocyte ghosts flocculated to the bottom of the tube. The reddish precipitate obtained by high speed centrifugation was washed thrice with liberal quantities of 0.01 M acetate buffer of pH 5.61. Both the distilled water-acetate buffer supernatant and the washings were checked for AChE activity, and none was found. Following the final washing the supernatant acetate buffer was carefully removed and the precipitate dissolved in 3.0 ml. of Krebs' buffer. To this mixture was added sufficient 0.01 N NaOH to adjust the pH to 7.3. Four-tenths milliliter of this solution was used for the AChE activity measurements.

Determination of Acetylcholinesterase Activity. AChE activity was determined manometrically by employing the Warburg technic. Measurements were carried out at 37.5° in Ringer-Krebs' bicarbonate medium. The final volume was 2.0 ml. Acetylcholine bromide and acetyl-β-methylcholine in a final concentration of 5×10^{-3} M were employed as substrates. The substrates had been recrystallized several times from absolute alcohol. The vessels were gassed with a mixture of 95 per cent N_2 and 5 per cent CO_2 for ten minutes. The substrate and cells were mixed and exactly three minutes were allowed for re-equilibration. Successive manometric readings were made at intervals of ten minutes for a total of thirty minutes. The first ten-minute interval was considered the most accurate measurement. This value was multiplied by six to give the rate per hour. Although a volume measurement of packed cells was used for the determinations, the final expression of enzyme activity was in terms of dry weight.

For the determination of the plasma cholinesterase, acetylcholine bromide was employed as a substrate. Two-tenths milliliter of plasma was used as the source of the enzyme. Acetyl-β-methylcholine was used in order to differentiate between the specific ("true") and the non-specific ("pseudo-") esterase of the plasma.

Determination of Phosphoglucomutase Activity. Phosphoglucomutase activity was determined by measuring the conversion of the acid-labile P of the 1-ester into the acid-stable P of the 6-ester [*16*].* The details of the method were as follows: The packed red cells to be tested were washed several times with large quantities of 0.85 per cent sodium chloride solution and then frozen and thawed three times. The enzyme solution (hemolyzed packed cells) to be tested was then kept at −20° for fifteen hours before use. Enzymatically prepared glucose-1-PO_4 was used as a substrate. This was prepared as a stock solution containing 2×10^{-2} M glucose-1-PO_4, and the pH was adjusted to 7.4. A stock solution containing 6×10^{-3} M Mg^{++} (as $MgCl_2$) and fresh 0.2 M histidine monohydrochloride was also prepared. A "triple-mix" was made by mixing all these solutions in equal proportions, and the pH was adjusted to 7.4. The triple-mix was then left in a constant temperature water bath at 30°. The reaction was started by adding 3.0 ml. of the hemolyzed red cells to 9.0 ml. of the triple-mix. Aliquots of 0.4 ml. were removed from the mixture at specific time intervals.

After incubation the reaction was stopped by the addition of 1.0 ml. of 10 per cent trichloracetic acid. Water was then added to bring the volume to 3.6 ml., and the reaction tubes were immersed in boiling water for precisely three minutes. The inorganic P formed during acid hydrolysis, which is equivalent to the unchanged 1-ester, was measured by a modification of the method of Fisk and Subbarow [*17*] using Kodak's semidine as a color developer. The acid-stable P represented the amount of glucose-6-phosphate formed. This was calculated from the difference in easily hydrolyzable P before and after incubation. The unit of activity was taken as the number of milligrams of acid-stable P formed per milliliter solution or per milligram of dry weight of the hemolyzed cells.

Method of Determining Dry Weight. Two-tenths milliliter of the packed red cells was pipetted care-

* We wish to express appreciation to Dr. Ernest E. McCoy of the Department of Microbiology for assistance in the determination of the phosphoglucomutase activity.

TABLE I

A SUMMARY OF ACETYLCHOLINESTERASE ACTIVITY IN NORMAL AND PNH ERYTHROCYTES

No. of Experiments (no. of separate samples)	Subjects	Whole Packed Cells			Top Layer of Packed Cells			Bottom Layer of Packed Cells			Ratio of Top:Bottom Layer in AChE Activity
		AChE Activity		Reticulocytes (%)	AChE Activity		Reticulocytes (%)	AChE Activity		Reticulocytes (%)	
		Q_{CO_2}*	% Change from Normal		Q_{CO_2}	% Change from Normal		Q_{CO_2}	% Change from Normal		
20 (20)	20 normal subjects	15.0 (11.0–18.9)†	.....	1.7	18.0 (15.2–20.0)	.....	3.0	14.0 (11.2–15.3)	.....	0.0	1.29
6 (1)	Case I	4.8 (3.6–6.0) Pa‡	−68.0	5.0	3.9 (3.0–4.8) Pa	−78.3	10.1	5.1 (4.0–6.8) Pa	−63.1	0	0.76
2 (1)	Case II	6.7 (6.5–7.0) Pa	−55.3	10.0	.....	.....	.....	.....	.....	.....	.....
5 (1)	Case III	10.0 (9.5–11.0) Pb§	−33.4	3.3	11.5 (9.9–13.2) Pb	−36.2	4.0	10.3 (9.5–10.9) Pb	−26.4	2.6	1.12
25 (17)	Case IV	7.2 (6.0–9.0) Pa	−52.0	4.0	8.8 (6.0–11.0) Pa	−50.2	5.3	4.8 (3.6–6.0) Pa	−64.5	0.8	1.83
6 (9)	Case V	5.05 (0.0–9.0) Pa	−66.4	8.0	2.5 (0.0–3.9) Pa	−86.1	45.4	7.6 (6.0–9.0) Pa	−44.8	7.0	0.32
7 (8)	Case VI	3.8 (1.0–6.8) Pa	−74.7	−10.2	2.2 (2.0–2.5) Pa	−87.8	46.1	3.7 (1.0–6.8) Pa	−73.6	2.0	0.59
4 (1)	1 normal subject‖	10.4 (8.9–11.5)	.....	.....	.....	.....	.....	.....	.....	.....	....
6 (1)	Case VII‖	3.3 (1.7–5.1) Pa	−68.3	.....	.....	.....	.....	.....	.....	.....	....
7 (1)	Case VIII‖	4.1 (4.0–4.9) Pa	−60.6	.....	.....	.....	.....	.....	.....	.....	....

* Q_{CO_2} = μl. CO_2 evolved per mg. dry weight per hour.
† Figures in parentheses represent the range of determined values.
‡ Pa = $p < 0.001$ } These values refer to significance of the variation from the values of normal red cells.
§ Pb = $p > 0.001$ }
‖ These specimens were processed by Dr. Carl F. Hinz, Jr. in Cleveland, Ohio and sent to Nashville in one shipment.

fully into small tin foil handmade cups. The cups were weighed empty and re-weighed after the red cell content reached a constant weight in a drying oven set at 110°.

Statistical Treatment of Data. The Student's t-test was employed to evaluate the significance of difference between mean values. All the differences referred to as significant had p values greater than, equal to or less than 0.001.

RESULTS

Acetylcholinesterase Activity of Normal and PNH Erythrocytes. A summary of the data on the AChE activity of normal and PNH cells is presented in Table I. In all patients with PNH the enzyme activity was markedly and significantly reduced. The enzyme activity was distinctly less than 50 per cent of normal in all cases except Case III. There was variation from time to time in the absolute amount of erythrocyte AChE in the patients with PNH although in virtually all instances the values remained significantly low. This variation could not be explained by the periodic occurrence of hemoglobinuric crises. In several cases serial determinations were performed during and after hemoglobinuric crises. Both absolute values and

TABLE II
THE ACETYLCHOLINESTERASE ACTIVITY OF NORMAL AND PNH ERYTHROCYTE STROMA

No. of Experiments	Subject	AChE Activity (μl. CO_2 per mg. dry weight per hour)	% Change from Normal
10	Case IV	52.1 (48–59)*	−54.4
	Normal	114 (101–143)	.....
4	Case V	34.2 (22–49)	−77.1
	Normal	149.0 (142–173)	.....
3	Case VI	8.8 (4.8–12)	−93.4
	Normal	132.8 (125–138)	.....
3	Case VII	33.4 (25–45)	−77.9
	Case VIII	43.3 (41–44)	−71.5
	Normal	151.7 (148–154)	.....

* Figures in parentheses represent the range of determined values.

ranges of AChE activity were not significantly different than at the time of freedom from hemoglobinuria. In the limited studies available to date, spontaneous variation in the degree of anemia (i.e., in the absence of recent transfusions) did not appear to greatly influence the erythrocyte AChE activity. In Cases IV and VI therapy with various steroid drugs (including amounts as large as 25 to 50 mg. of prednisolone administered per day) for weeks to months had no definite influence on the enzyme activity. One patient (Case VII) was receiving a methyltestosterone derivative and another (Case VIII) was taking dicumarol and prednisone at the time that markedly reduced erythrocyte AChE activity was determined.

In normal subjects top layer packed cells possessed significantly higher AChE activity (average 29 per cent) than bottom layer packed cells. (Table I.) (The reticulocyte concentrations were higher in the top layer packed cells.) Normal whole packed cells possessed both enzyme activity and reticulocyte concentrations intermediate between the values for the top and bottom layers. The ratio of top to bottom layer enzyme activity was 1.29 for normal cells.

Similar comparisons between top and bottom layer packed cells were carried out in samples of PNH cells. (Table I.) The ratios of enzyme activity of top to bottom layers of packed cells are shown in the far right-hand column in Table I. It is apparent that no regular or constant pattern was present from patient to patient. Nevertheless, in patients in whom many separate samples of packed cells were obtained at different times, the top layer-bottom layer ratios were relatively constant.

As in normal cells, the top layer-bottom layer enzyme activity ratios were greater than unity in Cases III and IV. However, in Cases I, V and VI the ratios were reversed. It is of particular interest that in these three cases the top packed red cell layers had concentrations of reticulocytes higher than in the other cases. Indeed, in Cases V and VI reticulocytes made up almost one-half of the cells in the top layer.

Acetylcholinesterase Activity of Erythrocyte Stroma. The AChE activity of stroma prepared from whole packed cells of normal subjects and those with PNH is indicated in Table II. All samples of PNH stroma showed extremely low enzyme activity. The greatest reduction was observed in Case VI. The per cent change from the normal in enzyme activity was essentially the same as that derived for intact erythrocytes. (Table I.) No AChE activity was found in the stroma-free supernatants. These results demonstrate that all the enzyme activity is localized in the stromal fraction. Thus our results are in agreement with the general opinion that the defect in PNH resides in the cell stroma.

Effect of Transfusion on Erythrocyte AChE in PNH. Transfusions of washed red cells regularly increased the erythrocyte AChE activity in aliquots of blood removed during the weeks following. Two representative experiments in which the packed red cells were also separated into top and bottom layers are shown in Table III. In Case III the study was carried out within a fortnight after 1 unit of packed cells and 5 units of washed cells had increased the patient's hematocrit from 5.5 to 40 per cent. In Case V the specimens were obtained within forty-eight hours after the infusion of 4 units of washed cells had raised the hematocrit from 21 to 37 per cent. Table III demonstrates that transfusions elevated the erythrocyte AChE of whole packed cells and of top and bottom layers of packed cells. The

TABLE III

EFFECT OF TRANSFUSIONS ON ERYTHROCYTE ACETYLCHOLINESTERASE ACTIVITY IN PNH

Subject	Condition of Transfusions	Whole Packed Cells			Top Layer of Packed Cells			Bottom Layer of Packed Cells		
		AChE Activity		Reticulocytes (%)	AChE Activity		Reticulocytes (%)	AChE Activity		Reticulocytes (%)
		Q_{CO_2}*	% Change from Normal		Q_{CO_2}	% Change from Normal		Q_{CO_2}	% Change from Normal	
20 normal subjects	None given	15.0 (11.0–18.9)	.....	1.7	18.0 (15.2–20.0)	.....	3.0	14.0 (11.2–15.3)	..	0.0
Case III	6 units of red cells given within fortnight prior to study increased PCV† from 5.5 to 40%	13.8	−8.0	1.9	13.5	−25	3.6	15.0	..	0.6
Case V	4 units washed cells given within 2 days prior to study increased PCV from 21 to 37%	12.9	−14.0	4.0	10.0	−44.4	16.9	14.8	..	1.9

* Q_{CO_2} = μl. CO_2 evolved per mg. dry weight per hour.
† PCV = volume of packed red cells in whole blood.

enzyme activity of the whole packed cells was in the lower ranges of normal. What is of particular interest is that while the enzyme activity of the bottom (reticulocyte-poor) layers was high-normal in value, the enzyme activity of the top (reticulocyte-rich) layers was relatively less increased and remained subnormal. This finding has a possible explanation in terms of the relative lifespans of the normal and PNH cells circulating in the patients with PNH who have received transfusions. Since the normal cells have a longer lifespan and orderly maturation and are not destroyed with abnormal rapidity by the patient with PNH, it would be expected that they would be found to a greater extent in the bottom (reticulocyte-poor) layer of older cells.

Effect of Oximes on AChE Activity of PNH Erythrocytes. Recently Grob and Johns [*18*] demonstrated that erythrocyte AChE which had been inhibited by organophosphorus anticholinesterase compounds could be moderately reactivated *in vitro* by the oxime, pyridine-2-aldoxine methiodide (2-PAM).* The effect of 2-PAM was tested on the red cells in Cases IV and V. The drug was incubated with the cells for fifteen minutes at 37.5°C. The AChE of the mixture was then determined. The final concentration of 2-PAM in the mixture was varied from 0.62×10^{-3} M to 5×10^{-10} M. No increase in the erythrocyte enzyme activity was noted in PNH cells mixed with 2-PAM.

PNH Family Studies. In Case V the erythrocyte AChE activity was normal in members of the patient's family. These included both parents, four siblings and three children. The results were also normal in the patient's wife. Clinical histories and blood counts were likewise normal in these family members.

Plasma Cholinesterase Activity. The results of plasma (non-specific, "pseudo-") cholinesterase determinations in Cases I, III, IV and V are shown in Table IV. In all four patients the values were below the average of twelve samples from normal subjects. In Cases I and III the reduction in plasma cholinesterase was striking. In Case I the plasma cholinesterase determination was carried out in February 1958, at the time of clinical and biochemical evidence of marked hepatocellular damage (see Case I [*14*]). In Case III the plasma enzyme value was determined at the time of severe anemic relapse (hematocrit 5.5 per cent). With the exception of diminished prothrombic activity, none of the other biochemical tests of liver function were abnormal at that time (see Case III [*14*]).

Phosphoglucomutase Activity of PNH Cells. Data on the phosphoglucomutase activity of the red cells in Case V are illustrated in Figure 1. The

* 2-PAM was kindly provided by Dr. Henry J. Wills, Chemical Corps Medical Laboratories, Army Medical Center, Maryland.

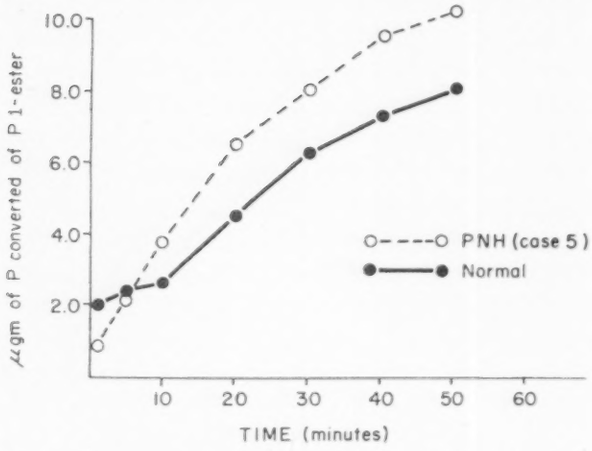


FIG. 1. Phosphoglucomutase activity in PNH and normal erythrocytes at 30°C.

enzyme activity was not reduced. In fact it was slightly higher than in the normal cells used as the control in this experiment.

TABLE IV
PLASMA CHOLINESTERASE ACTIVITY IN PNH

Subject	No. of Experiments (no. of separate samples)	Plasma Cholinesterase Activity (μl. CO_2 evolved per 0.2 ml. of plasma per hour)	% Change from Normal
Normal . .	12 (12)	323	. . . .
Case I . . .	4 (1)	146	−55
Case III . .	4 (1)	180	−44
Case IV . .	10 (4)	273	−15
Case V . . .	10 (4)	249	−23

COMMENTS

Erythrocyte acetylcholinesterase activity was strikingly and consistently reduced in eight cases of PNH. The enzyme activity was below 50 per cent of normal in all but one case (Case III).

Erythrocyte AChE activity has been studied in many anemias and experimental conditions [*19–22*], and has been noted to be slightly reduced in some cases of anemia associated with renal disease [*21*], and in a case each of myelosclerosis [*21*] and aplastic anemia [*22*]. In pernicious anemia the erythrocyte AChE has been reported to be normal or low [*20–22*]. De Sandre and Ghiotto reported an average reduction of 8.7 per cent in pernicious anemia [*21*]. Serial changes in erythrocyte AChE activity have been used to assess accelerated erythropoiesis [*20*]. More impressive than the slight depression in enzyme activity during pernicious anemia relapse is the temporary "supranormal" rise following specific therapy [*20,21*]. A slight increase in enzyme activity has been noted in some cases of iron deficiency anemia [*21*]. The occurrence of increased erythrocyte AChE activity in hemolytic anemias, in general, has been both claimed and denied. In none of these disorders was the AChE enzyme activity found to be strikingly and consistently reduced.

Preliminary results of a survey of patients with miscellaneous blood dyscrasias revealed no marked alteration in erythrocyte AChE activity in one or several patients with each of the following: iron deficiency anemia, iron deficiency anemia under treatment, pernicious anemia in remission, megaloblastic anemia associated with dilantin therapy, acquired hemolytic anemia, congenital non-spherocytic hemolytic anemia, aplastic anemia, "pure red cell anemia," myeloid metaplasia, myelophthisic anemia, di Guglielmo's syndrome (?), sickle cell trait, sickle cell anemia, polycythemia vera, acute and chronic myeloid leukemia, acute and chronic lymphatic leukemia, Hodgkin's disease, giant follicular lymphoma, "idiopathic" thrombocytopenic purpura, and thrombotic thrombocytopenic purpura in remission. *Thus only in PNH has there been both consistent and striking reduction in erythrocyte AChE activity.*

The situation regarding Case III requires special comment since the erythrocyte AChE activity was only moderately reduced (−33 per cent) relative to the reduction in the other patients with PNH (−52 to −74 per cent). This finding may be explained by the severely hypoplastic marrow in this instance [*14*]. Nelson and Bruce reported on a patient presenting initially with the classic findings of PNH but in whom manifestations of aplastic anemia subsequently dominated the clinical picture [*23*]. During the latter period the Ham and Crosby tests were only sporadically positive. The authors suggest that "the hypoplastic marrow is still capable of producing cells with the erythrocyte defect and

the reduced production of abnormal cells, which usually forms only a proportion of the whole, is responsible for the technically negative results." Such a mechanism could explain the fact that the reduction of red cell AChE activity in Case III was less than in the other patients with PNH who had cellular marrows.

Although the bone marrow is usually hypercellular in PNH, it has been claimed that there is impaired functional reserve capacity [*2*]. Thus, in addition to the increased destruction of red cells, there is what might be termed a "functional hypoplasia" or relative marrow failure [*24*]. Low erythrocyte AChE activity was reported in one patient with aplastic anemia [*22*], and the activity of this enzyme has been taken as a measure of erythropoiesis [*20*]. The relative marrow failure in PNH might have been responsible for the reduced enzyme activity in this instance but evidence that such is not the case can be cited from several sources. In Case III the patient had the most hypoplastic marrow and greatest transfusion requirements [*14*] but the erythrocyte AChE activity showed the *least* reduction. Furthermore, in our studies applastic anemia and other disorders with marrow failure did not have any marked alteration in enzyme activity. Finally, in some patients with PNH the specimens with greatest reticulocyte concentrations had extremely low enzyme activity (Cases V and VI, Table I).

The AChE activity of top (reticulocyte-rich) and bottom (reticulocyte-poor) layers of *normal* packed erythrocytes was determined. That the enzyme activity of the reticulocyte-rich upper layer was higher is an indication that it is normally greater in young cells. Similar findings were reported in rats by Pritchard [*19*]. Sabine also noted a higher concentration of the enzyme in young cells [*20*]. In her work the AChE activity of the top layer of packed cells was 36 per cent greater than that of the bottom layer, and the difference was greatest when the reticulocyte count was the highest. On the other hand, De Sandre and Ghiotto reported that the erythrocyte AChE in anemias bore no direct relation to the number of reticulocytes [*21*]. These investigators, however, did not make separate observations on top and bottom layers of packed cells.

In confirmation of the results of Sabine [*20*] and Pritchard [*19*], our experiments demonstrated higher AChE in the top (reticulocyte-rich) portions of normal packed cells. (Table I.) No consistent pattern was observed with PNH cells. (Table I.) In Cases III and IV the ratio of top to bottom layer enzyme activity was greater than 1.0, as in normal cells. On the other hand, the ratios were strikingly reversed in the other patients tested (Cases I, V and VI). Another interesting point is that even though the top layers of packed red cells in Cases V and VI consisted approximately of 50 per cent reticulocytes, the AChE enzyme activity was extremely low. In these two patients the enzyme activity apparently increases as the cell matures, but whether this is due to enzyme synthesis or to the appearance and disappearance of inhibitors or activators cannot presently be stated. These data show, however, that immature red cells with low AChE activity are formed. In several preliminary experiments very low AChE activity was noted in cellular PNH marrow aspirates. These findings suggest that PNH red cells may be formed with deficient AChE activity, and that this defect is not necessarily acquired during the intravascular sojourn of the PNH red cells.

In several of the patients with PNH the erythrocyte AChE activity fluctuated markedly. This finding remains unexplained. Possibly it is related to the known fluctuations in the natural course of the disorder. The current investigation presents no absolute evidence for the presence of an inhibitor of AChE activity. No heat-labile inhibitor could be destroyed or eluted by heating the PNH cells at several temperatures (40° to 57°C.) for periods up to one hour. 2-PAM, which is capable of moderately reactivating red cell cholinesterase inhibited by organophosphorus compounds, did not affect the reduced activity of PNH erythrocytes under the experimental conditions cited. Furthermore, the addition of PNH plasma to normal cells *in vitro* produced no significant inhibition of the enzyme. However, none of our studies preclude the possibility of an inhibitor of erythrocyte AChE in PNH, particularly an inhibitor bound firmly to the enzyme. Additional studies are in progress to determine whether or not such an inhibitor exists.

Three of our six patients were farmers, and one was a gardener [*14*]. Although a reliable history of exposure to fertilizers and insecticides was documented in only one patient, such exposure may have occurred in all four. Some insecticides possess anticholinesterase activity [*25*]. On the other hand, the occupational distribution in our small series probably merely

reflects the fact that the two hospitals concerned draw heavily on agricultural regions of Tennessee for their patient census. Furthermore, two of our patients (Cases I and II) have not attempted farming or gardening for many years, and their disease process continues unabated.

When normal cells were transfused into patients with PNH, the AChE activity of the transfused cells was not reduced. This is further evidence against the presence of a circulating inhibitor. A temporary enhancement of activity was also noted when several washed red cell transfusions were administered to the patient with PNH reported by the Italian workers [*26*]. The present results are consistent with other transfusion studies. Normal cells have been shown to have a normal lifespan in patients with PNH. Furthermore, if the normal cells are separated from the patient's cells weeks after transfusion, they do not undergo spontaneous lysis *in vitro* as do PNH cells [*1*].

The transfusion data in Case III could be readily interpreted as the result of simple admixture of PNH and normal red cells. (Table III.) However, the data in Case V and preliminary data in other cases suggest that the degree of increase in erythrocyte enzyme activity might be greater than expected from simple admixture of the two types of cells. Furthermore, in Case V multiple transfusions given on the same day abolished the hemoglobinuria on repeated occasions [*14*]. Others have shown that transfusions simultaneously halted the hemoglobinuria and decreased the absolute number of cells susceptible to *in vitro* hemolysis in acidified serum [*27*]. These observations suggest the possibility that the transfused normal cells may in some manner influence the AChE activity of the most "susceptible" cells. More extensive experiments employing radioisotope tagging of infused normal erythrocytes are being carried out.

The precise significance of the low red cell AChE activity in PNH remains unexplained. Ever since AChE was first demonstrated in the red cell of man, much interest has centered around the question of the function of this enzyme with reference to the erythrocyte. The enzyme resides exclusively in the stromal fabric. The enzyme activity of stroma prepared from PNH erythrocytes was strikingly low. Several investigators have reported that the PNH stromal fabric is patchy and pitted [*9–11*]. This interesting observation may be related to the deficiency of AChE activity of these cells. Cheli and Dianzani, for example, demonstrated that in experimental immune hemolytic anemia in guinea pigs there was both a reduction in erythrocyte AChE activity and "irregular roughness and porosity" of the red cell stroma [*28,29*].

Cholinesterase inhibitors have been shown to produce an increase in the permeability of erythrocytes [*30*]. Such studies suggest that maintenance of the integrity of erythrocytes depends in some manner on the activity of the acetylcholine-cholinesterase system. Holland immunized rabbits with bovine erythrocyte stroma and stromal fractions [*31*]. Evidence was presented suggesting that the AChE of bovine red cell stroma was antigenic, stimulating the production of antibodies against bovine AChE in the rabbit. This antibody in turn was considered capable of hemolyzing bovine erythrocytes. Using other immunological methods, Holland prepared a specific inhibitor of AChE. This antibody also brought about changes in red cell permeability. The Italian workers studied the role of AChE in relation to red cell permeability, stressing the importance of the enzyme with reference to erythrocyte shape, volume and surface change [*21*]. Their results also suggest a possible relationship between the activity of the enzyme and stromal phospholipid turnover. On the other hand, the absence of measurable AChE activity in the erythrocytes of certain mammalian species has led some investigators to conclude that the enzyme system cannot play a universal role in maintaining cell permeability [*32*].

There is evidence that the acetylcholinesterase system may be involved in the permeability of other tissues. Physostigmine, carbaminoyl choline and mecholyl have been found to produce permeability changes of the blood-aqueous barrier when instilled into the eye [*33*]. Following the administration of prostigmine, an anticholinesterase, to patients with myasthenia gravis, changes in serum and muscle potassium have been noted [*34*]. Other investigators have shown that prostigmine decreases the serum potassium in dogs and cats [*35*]. There is also evidence suggesting that the AChE system is involved in permeability changes of nerve cells [*36*].

In order to determine whether or not a general poverty of enzyme activity exists in PNH red cells, the activity of one of the enzymes of the

glycolytic scheme was measured. The enzyme chosen was phosphoglucomutase. The activity of this enzyme was not reduced. Other enzymes are under investigation in order to determine whether or not reduced AChE activity of PNH cells is the only enzyme defect.

It has been postulated that the white cells and platelets in PNH have the same stromal defect as the red cells [*2*]. Rather convincing histochemical and manometric studies have demonstrated that normal human platelets contain no measurable cholinesterase [*32*]. Thus platelets apparently do not share the defect in acetylcholinesterase activity in PNH.

Since the erythrocyte AChE was normal in nine family members of one patient (Case v), our studies provide no evidence for a biochemical-genetic basis for PNH. This is in agreement with the general concept regarding this disease [*2,37*]. Nevertheless, these studies do not absolutely exclude the possibility of genetic transmission with "low penetrance" of other biochemical abnormalities. Only further biochemical study of the PNH cell will answer this question.

The non-specific plasma cholinesterase also was decreased in the four cases of PNH studied. (Table iv.) In two instances the reduction was striking. In Case i this could be readily explained by complicating marked hepatocellular damage. No explanation is at hand in Case iii.

Markedly reduced erythrocyte AChE activity can be added to the diagnostic armamentarium for the detection of patients with PNH. For the present, the specificity of the test seems to be of relatively high order. The sensitivity in detecting patients with PNH awaits the test of time and further experience.

There is currently great interest in organophosphorus inhibitors of cholinesterase (e.g., war gases). The cholinesterase systems and their inhibitors are being intensively studied. Although nerve tissue apparently bears the brunt of the deleterious effects of organophosphorus anticholinesterases [*38*], such human tissue obviously is not readily available for *in vitro* investigation. By contrast, red cells of the patient with PNH can be easily obtained for such study. Whether the defective enzyme activity of the PNH red cell is due to a deficiency *per se* or to the action of inhibitors, this abnormal cell should be an excellent tool for gaining further information regarding the complexities of the acetylcholine-cholinesterase system.

SUMMARY

Markedly reduced erythrocyte acetylcholinesterase activity was demonstrated in all eight cases of paroxysmal nocturnal hemoglobinuria studied. Consistent reduction of this degree has not been noted in other blood dyscrasias, either in studies cited in the literature or in our own investigations.

The defect was localized to the stroma of the PNH red cell. The enzyme activity of reticulocytes was markedly impaired, indicating that the immature cells were formed with defective acetylcholinesterase. The activity of normal cells was not reduced following transfusion into patients with PNH.

No evidence was found for a circulating inhibitor of acetylcholinesterase or for one which could be readily eluted from the PNH erythrocyte membrane. However, our studies do not exclude the possibility of an inhibitor, particularly one bound firmly to the enzyme.

In the one case in which a family study was carried out, normal erythrocyte acetylcholinesterase activity was present in all members tested.

The previous work of many investigators has suggested that erythrocyte acetylcholinesterase plays an important role in the preservation of the integrity of the red cell. The significance of the defective enzyme activity in the PNH cell is discussed in this connection.

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A Comparative Study of Four Prothrombinopenic Anticoagulant Drugs*

I. Properties

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THE technical difficulty of maintaining smooth control of anticoagulant levels has led to a search for the "ideal" anticoagulant. Many drugs have had clinical trials since the introduction of bishydroxycoumarin in 1942, but the superiority of one drug over the others has not been demonstrated in a well controlled study. When the drugs being studied were administered concurrently under comparable conditions, no significant differences were apparent. Few such studies have been reported [*1–5*].

A comparative study was undertaken of four commonly used and representative prothrombinopenic drugs, bishydroxycoumarin (dicumarol), warfarin (prothromadin), phenindione (Hedulin®) and diphenadione (Dipaxin®).† Bishydroxycoumarin and warfarin are coumarin derivatives; phenindione and diphenadione are inanedione derivatives. All act similarly by depression of the hepatic synthesis of proconvertin and prothrombin [*6*].

It soon became apparent that certain properties of these agents could best be evaluated in a relatively healthy group of subjects in whom there was no therapeutic indication for anticoagulant therapy. The studies were divided into three phases. The purpose of the first was to gain information regarding the onset of action, peak effect, duration of effect, and variability of effect of the four drugs; the purpose of the second was to compare the conventional induction schedule for bishydroxycoumarin with a more radical dosage program; and of the third to compare the optimum induction dosage programs of the four drugs.

† Prothromadin was provided for this study by the G. F. Harvey Co., Saratoga Springs, New York and Dipaxin by the Upjohn Co., Kalamazoo, Michigan.

METHOD

1. Twenty subjects with prothrombin activity over 80 per cent and no evidence of liver disease or bleeding tendency were divided into four equal groups. Members of each group were given a single large oral dose of one of the four prothrombinopenic drugs. The dosages used were bishydroxycoumarin 600 mg., diphenadione 60 mg., phenindione 600 mg., and warfarin 90 mg. These were thought at the time to be approximately comparable. The prothrombin activity was then determined at eight-hour intervals up to the 108th hour by a modified Quick one-stage technic using Simplastin.® The results were reported in seconds and converted to per cent of control prothrombin activity.

2. Twelve subjects were divided into two groups. Those in one group were given 300 mg. of bishydroxycoumarin the first day, 200 mg. the second day and 100 mg. the third day. Those in the second group were given 600 mg. of bishydroxycoumarin the first day and 150 mg. the second day. In addition to the control level, prothrombin activity was determined at 16, 40, 64, 88 and 108 hours after the initial dose.

3. Forty-eight subjects were divided into four groups. Induction programs which were considered on the basis of clinical experience to be the best for each drug were used. (Table 1.) The dose varied slightly according to the initial prothrombin activity, but in each case one large initial dose was given followed by a maintenance dose. The prothrombin activity was determined at twenty-four-hour intervals starting with the sixteenth hour.

* From the Medical Service and the Medical Research Laboratory, Veterans Administration Hospital, Philadelphia, Pennsylvania.

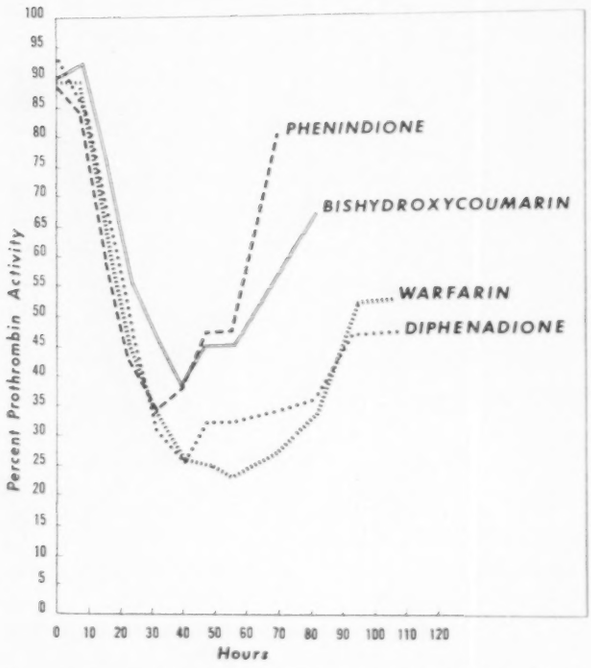


FIG. 1. Per cent of prothrombin activity after a single large dose of four prothrombin depressant agents. Each curve represents average values in five patients.

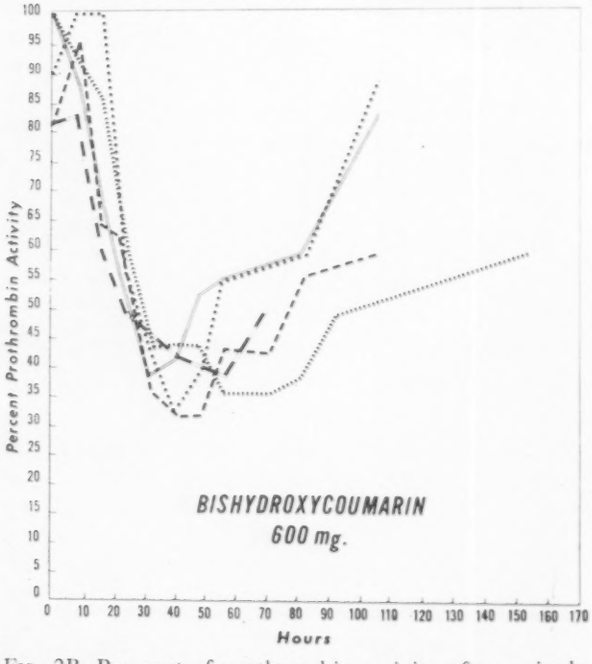


FIG. 2B. Per cent of prothrombin activity after a single large dose of bishydroxycoumarin in each of five patients.

RESULTS

Eight hours after the administration of a single large dose of any of the drugs no depression of prothrombin activity was present. (Fig. 1.) There was significant depression in all four

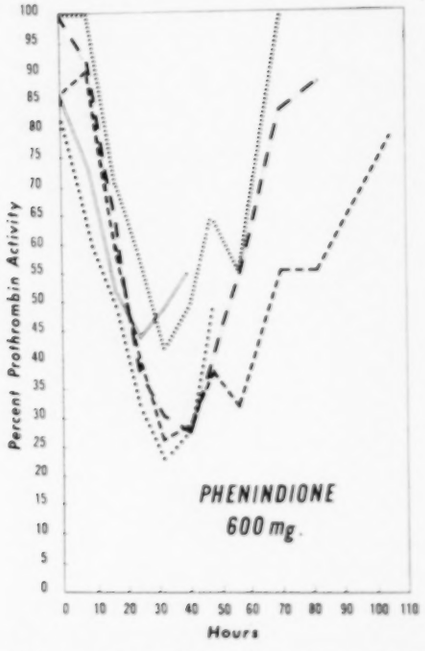


FIG. 2A. Per cent of prothrombin activity after a single large dose of phenindione in each of five patients.

groups at sixteen hours, indicating that the onset of action of all four drugs occurred between the eighth and sixteenth hour. The peak effect in the group given phenindione was obtained at thirty-two hours, while that in the other three groups occurred at forty hours. The duration of effect appeared to be least for bishydroxycoumarin and longest for warfarin. This difference may, however, be more apparent than real. The doses of the drugs were probably not comparable, since the depression of prothrombin activity was much greater with the 90 mg. dose of warfarin than with 600 mg. of bishydroxycoumarin. Comparison of the curve of prothrombin activity in all of the patients receiving the

TABLE I
RECOMMENDED INITIAL DOSE

Drug	Dose with Control Prothrombin Activity of		
	80–100 Per cent	60–80 Per cent	50–60 Per cent
Bishydroxycoumarin	650 mg.	600 mg.	550 mg.
Diphenadione	60 mg.	55 mg.	50 mg.
Phenindione	500 mg.	450 mg.	400 mg.
Warfarin	75 mg.	70 mg.	60 mg.

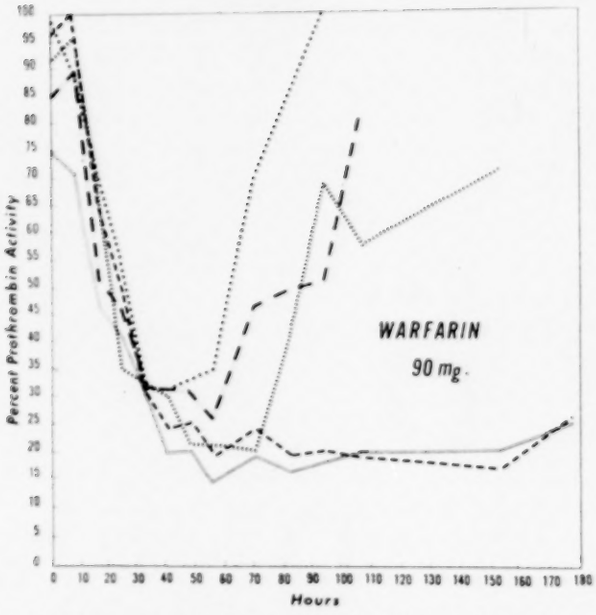


FIG. 2C. Per cent of prothrombin activity after a single large dose of warfarin in each of five patients.

same drug (Fig. 2) shows that the onset of action, peak effect and degree of prothrombin activity depression are fairly uniform among the patients in each group, but the duration of effect is quite variable.

Comparison of the conventional dose of bishydroxycoumarin with our more radical induction program revealed that none of the subjects who received the conventional doses were within the therapeutic range (10 to 30 per cent prothrombin activity) until sixty-four hours after the initial dose. (Table II.) All six subjects who received the larger doses were in the therapeutic range within sixty-four hours and three of them within forty hours after the initial dose. In none

TABLE II
COMPARISON OF INDUCTION DOSAGE SCHEDULES OF BISHYDROXYCOUMARIN

Dose	Percentage of Patients in Therapeutic Range at	
	Forty Hours	Sixty-four Hours
300 mg. first day 200 mg. second day	0	67
600 mg. first day 100 mg. second day	50	100

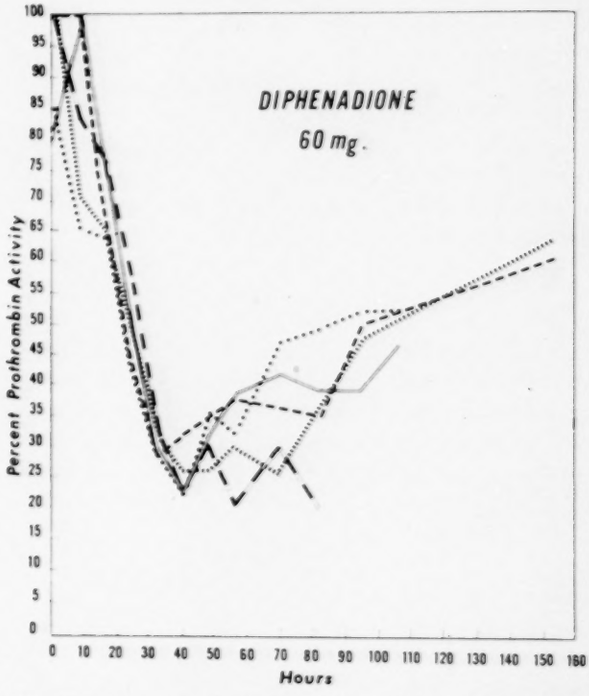


FIG. 2D. Per cent of prothrombin activity after a single large dose of diphenadione in each of five patients.

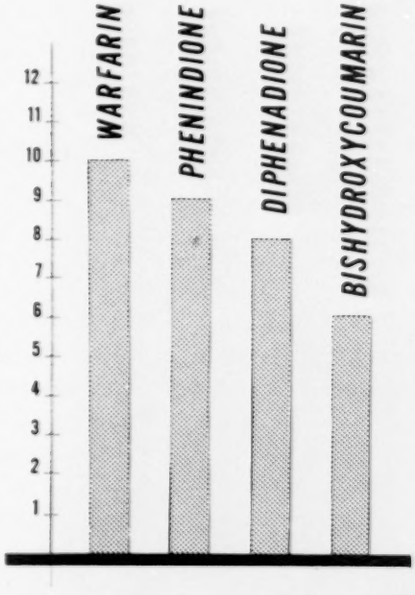


FIG. 3. Bar graph represents number of patients in therapeutic range forty hours after "optimum" initial dose of four anticoagulants. Twelve patients were treated with each agent.

was the prothrombin activity depressed below the lower limit of the therapeutic range.

Comparison of the "optimum" induction program for each of the four drugs showed no striking differences. (Fig. 3.) Of the twelve sub-

jects who received warfarin, ten were in the therapeutic range forty hours after the initial dose. Nine patients given phenindione, eight given diphenadione and six given bishydroxycoumarin were in the therapeutic range at forty hours. Two of the twelve subjects who received warfarin had a prothrombin activity less than 10 per cent at sixty-four hours.

COMMENTS

Variation in the dosage requirements of a prothrombinopenic drug may be related to one or more of three factors. These are the absorption of the drug, the sensitivity of the liver to its prothrombinopenic effect, and the rate of catabolism of the agent. Although the effect of a single large dose of any of the agents studied was fairly uniform in its initial prothrombin depressant effect, there were wide variations in the duration of the effect. This suggests that the rate of metabolic breakdown and excretion is the most important determinant of dosage. It also suggests that more uniform results in clinical anticoagulant therapy might be anticipated if an initial dose large enough to bring the patient into the therapeutic range were used.

SUMMARY

Eighty subjects in whom there was no therapeutic indication for anticoagulant therapy were given four prothrombinopenic agents, bishydroxycoumarin, diphenadione, phenindione and warfarin. The onset of action of all four drugs was between the eighth and sixteenth hour following the administration of a single large dose. The peak effect for phenindione was obtained in thirty-two hours, and for the other three drugs in forty hours. The extent of depression was reasonably uniform among subjects receiving the same drug but the duration of effect was quite variable.

The findings suggest that an induction program consisting of a single large loading dose followed by a maintenance dose might be practical and safe for all four drugs.

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A Comparative Study of Four Prothrombinopenic Anticoagulant Drugs*

II. Clinical Study

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A PRELIMINARY appraisal of four commonly used and representative prothrombinopenic drugs, bishydroxycoumarin (dicumarol), warfarin (prothromadin),‡ phenindione (Hedulin®) and diphenadione (Dipaxin®)‡ was carried out in a relatively healthy group of subjects in whom there was no therapeutic indication for anticoagulant therapy [*1*]. This study provided information about the action of these agents that seemed to have practical clinical implications. Because of the widely divergent reports in the literature as to the relative merits and disadvantages of these agents [*2–9*], and the paucity of well controlled studies of more than one agent administered concurrently under comparable conditions, an evaluation of the same four anticoagulants‡ was undertaken in patients requiring anticoagulant therapy.

METHOD

Two hundred eighty-seven patients were studied. One hundred seventy-one patients had myocardial infarction, forty-eight had pulmonary infarction, forty-two thrombophlebitis, eleven intracardial mural thrombosis and embolism, and fifteen miscellaneous indications. (Table I.) Most of the patients received concentrated aqueous heparin subcutaneously during the induction of hypoprothrombinemia. All anticoagulants were ordered by the same three physicians. The initial dose of the prothrombinopenic agent and all subsequent doses were administered daily at 4 P.M., and blood was drawn for prothrombin determination at 8 A.M., so that the interval between the administration of the dose and the withdrawal of blood was uniformly sixteen hours. Prothrombin activity was determined by a modification of the Quick one-stage method, using Simplastin.® The results were reported in seconds and converted to per cent of control prothrombin activity. An attempt was made to maintain the prothrombin activity in a therapeutic range between 10 and 30 per cent. Prothrombin determinations were performed daily until a stable level in the therapeutic range was reached, usually a period of four to ten days. The frequency of the determinations was then reduced to three times a week.

‡ Prothromadin was provided for this study by the G. F. Harvey Co., Saratoga Springs, New York and Dipaxin by The Upjohn Co., Kalamazoo, Michigan.

RESULTS

Two hundred eighty-seven patients were maintained on anticoagulant therapy for a total of 7,165 patient days, an average of twenty-five days per patient. Of these 7,165 days, 637 were required to reach therapeutic levels, an average induction period of 2.2 days per patient.

Induction Therapy. One of the important attributes of a satisfactory anticoagulant is rapid onset of therapeutic effect. With conventional dosage schedules of bishydroxycoumarin (300 mg. the first day, 200 mg. the second day), a long induction period has been one of the major disadvantages of this drug. After some experimentation it was determined that with a larger initial dose, more rapid development of therapeutic prothrombin levels could be achieved. A comparison of patients treated by the conventional dosage schedule with patients given an initial dose of more than 500 mg. showed that only 29 per cent of the first

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TABLE I
NUMBER OF CASES AND DIAGNOSES

Diagnosis	Patients (no.)	Average Age (yr.)	Treatment (average no. days)
Bishydroxycoumarin (77 patients)			
Myocardial infarction	45	58	29
Pulmonary infarction	9	52	19
Thrombophlebitis	20	50	17
Embolism	0	..	..
Miscellaneous	3	65	19
Diphenadione (74 patients)			
Myocardial infarction	45	56	31
Pulmonary infarction	13	41	19
Thrombophlebitis	9	47	17
Embolism	3	61	28
Miscellaneous	4	63	18
Phenindione (69 patients)			
Myocardial infarction	38	60	27
Pulmonary infarction	13	52	19
Thrombophlebitis	6	47	16
Embolism	6	54	16
Miscellaneous	6	59	24
Warfarin (67 patients)			
Myocardial infarction	39	53	27
Pulmonary infarction	16	51	23
Thrombophlebitis	8	49	13
Embolism	0	..	..
Miscellaneous	4	54	21

group of patients, but 71 per cent of the second group, were in the therapeutic range at forty hours. (Table II.) This difference is statistically significant at the .01 level. The safety of this larger initial dose is demonstrated by the fact that of the seventeen patients receiving more than 500 mg. initially only one had a prothrombin activity less than 10 per cent at sixty-four hours. This was back in the therapeutic range at eighty-eight hours without incident.

It became apparent that few patients could be brought into the therapeutic range within sixteen hours but that most patients could be brought into the therapeutic range in sixty-four hours with any of the four drugs. A comparison of the drugs as to ease and rapidity of induction was therefore based upon the number of patients brought into the therapeutic range within forty hours by a large initial dose. (Table II.) Only patients whose initial prothrombin level was above 60 per cent were considered. At forty hours, all the patients treated with phenindione, 84 per cent of those treated with diphenadione, 72 per cent of those treated with warfarin and 71 per cent of those treated with bishydroxycoumarin were in the therapeutic range. Of 134 patients given large initial doses 82 per cent were in the therapeutic range within forty hours.* Only five patients, three treated with diphenadione, one treated with bishydroxycoumarin and one with warfarin, had a prothrombin activity less than 10 per cent at sixty-four hours. All these returned to the therapeutic range spontaneously by eighty-eight hours.

Maintenance Therapy. An important property of an anticoagulant drug is the facility with which patients can be kept in the therapeutic range with minimal variation in maintenance dose from day to day. A desirable but less important property is the lack of variation in maintenance dose from patient to patient. On the basis of total patient days, patients were maintained in the therapeutic range (10 to 30 per cent) with bishydroxycoumarin 87 per cent of the time, with diphenadione 87 per cent, with warfarin 80 per cent and with phenindione 76 per cent. (Table III.) These figures are necessarily weighted by the larger contribution to the total number of days by the patients who were under treatment longest. The contribution of each patient to these data is equalized somewhat by considering instead the percentage of the time each patient was in the therapeutic range. When the same series of cases is considered in this way, 98 per cent of the group treated with bishydroxycoumarin, 86 per cent of the group treated with diphenadione, 77 per cent of the group treated with warfarin and only 71 per cent of the group given phenindione were in the therapeutic range more than 70 per cent of the time, representing a fairly satisfactory degree of control. (Table IV.) Bishydroxycoumarin was slightly but significantly better than diphena-

* Since the completion of the present study seventy-five additional patients have been treated with similar large initial doses of prothrombinopenic drugs. Eighty-three per cent have been brought into the therapeutic range within forty hours and only one patient has had a prothrombin level (transiently) below 10 per cent.

TABLE II
INDUCTION THERAPY

Drug and Dosage	Patients (no.)	Per cent in Therapeutic Range (10–30 per cent) at:				
		16 Hours	40 Hours	64 Hours	88 Hours	112 Hours
Bishydroxycoumarin 300 mg. first day / 200 mg. second day	38	3	29	71	97	100
Bishydroxycoumarin 500–650 mg. first day / 100–200 mg. second day	17	6	71	89	95	100
Phenindione 350–500 mg. first day / 100–200 mg. second day	25	8	100	..	...	...
Diphenadione 40–60 mg. first day / 10–20 mg. second day	57	19	84	95	97	100
Warfarin 65–80 mg. first day / 10 mg. second day	35	6	72	98	100	...

TABLE III
MAINTENANCE THERAPY

Drug	Patients (no.)	Total Days of Therapy (no.)	Days for Induction (no.)	Days in Therapeutic Range (no.)	Days Out of Therapeutic Range (no.)	Days in Therapeutic Range (%)
Bishydroxycoumarin	77	1,908	220	1,477	211	87.5
Diphenadione	74	1,890	145	1,525	220	87.4
Warfarin	67	1,585	140	1,160	285	80.3
Phenindione	69	1,782	132	1,257	393	76.2
Totals	287	7,165	637	5,419	1,109	82.9

dione ($P < 0.05$), and considerably better than the other drugs in this respect.

The daily maintenance dose of each drug showed rather wide variations both from day to day and from patient to patient. (Table v.) To evaluate daily fluctuations in dosage for individual patients, a dose was arbitrarily considered "stable" on any day that it was within 30 per cent above or below the average daily dose for that patient. In patients receiving diphenadione 76 per cent of the maintenance days were in the "stable" range. With phenindione 76 per cent, with bishydroxycoumarin 70 per cent and with warfarin 63 per cent of the days were "stable." (Table VI.) Using the same criteria for "stability," but employing the percentage of stable days for each patient to avoid weighting of the data by the long term patients, 67 per cent of the patients receiving diphenadione, 66 per cent of the patients receiving bishydroxycoumarin, 61 per cent of the patients receiving phenindione and only 40 per cent of the patients receiving warfarin were in the "stable" range more than 70 per cent of the time.

TABLE IV
MAINTENANCE THERAPY

Drug	Percentage of Patients in Therapeutic Range			
	More Than 90 Per cent of Time	More Than 80 Per cent of Time	More Than 70 Per cent of Time	More Than 60 Per cent of Time
Bishydroxycoumarin	54	80	98	99
Diphenadione	59	73	86	90
Warfarin	38	53	77	83
Phenindione	32	52	71	78

TABLE V
SIZE OF AVERAGE MAINTENANCE DOSE

Drug	Range (mg.)	Average (mg.)
Bishydroxycoumarin	43–221	90.7
Diphenadione	1.7–13.8	6.9
Phenidione	36–204	97.6
Warfarin	3.1–21.4	7.7

TABLE VI
DAYS OF STABLE MAINTENANCE DOSE (WITHIN 30 PER CENT OF AVERAGE DAILY DOSE)

Drug	Maintenance Therapy (days)	Stable Days (no.)	Stable Days (%)
Diphenadione	1,678	1,269	76
Phenindione	1,620	1,183	73
Bishydroxycoumarin	1,628	1,133	70
Warfarin	1,400	888	63

TABLE VII
STABILITY OF MAINTENANCE DOSE

Drug	Percentage of Patients with Stable Maintenance Dose			
	More Than 90 Per cent of Time	More Than 80 Per cent of Time	More Than 70 Per cent of Time	More Than 60 Per cent of Time
Diphenadione	25	50	67	81
Bishydroxycoumarin	26	48	66	74
Phenindione	29	36	61	74
Warfarin	14	27	40	56

TABLE VIII
UNIFORMITY OF MAINTENANCE DOSE

Drug	Percentage of Patients with Average Maintenance Dose Deviating from Group Average by		
	Less Than 20 Per cent	Less Than 40 Per cent	Less Than 60 Per cent
Warfarin	46	79	97
Bishydroxycoumarin	41	84	96
Phenindione	34	68	85
Diphenadione	35	72	84

(Table VII.) All three of the other drugs were significantly better than warfarin ($P < 0.01$), but not significantly different from each other.

Variation in the average maintenance dose of each drug from patient to patient was evaluated according to the deviation of each patient's average maintenance dose from that of the group. (Table VIII.) The least variation was found with warfarin and bishydroxycoumarin. This difference is significant at the .02 level. If the variation of dosage in milligrams is considered rather than percentage deviation, 84 per cent of the group receiving warfarin, 81 per cent of the group receiving bishydroxycoumarin, 74 per cent of the group receiving diphenadione and 69 per cent of the group receiving phenindione were within comparable dosage ranges of 4 to 10 mg. for warfarin and diphenadione and 50 to 125 mg. for bishydroxycoumarin and phenindione. (Table IX.)

Dosage requirements have been reported to vary with the season of the year and with the disease under treatment. Analysis of this series suggests a higher dosage requirement in winter, and in patients with thrombophlebitis. The differences are so slight and the overlapping so great that this information is not applicable to clinical anticoagulant therapy in individual patients.

Restoration of Normal Prothrombin Levels. The rapidity with which prothrombin levels return to normal after withdrawal of the drugs was studied. Comparison of a group of patients whose prothrombin activity was in the therapeutic range (10 to 30 per cent) on the last day of therapy shows a gradual loss of pharmacologic

TABLE IX
MAINTENANCE DOSE REQUIREMENTS

Drug	Percentage of Patients Requiring Maintenance Dose		
	Less Than 4 mg. (W, D) 50 mg. (B, P)	4 to 10 mg. (W, D) 50 to 125 mg. (B, P)	More Than 10 mg. (W, D) 125 mg. (B, P)
Warfarin (W)	5	84	11
Bishydroxycoumarin (B)	6	81	11
Diphenadione (D)	7	74	17
Phenindione (P)	8	69	20

TABLE X
PERCENTAGE OF PATIENTS WITH NORMAL PROTHROMBIN LEVEL (ABOVE 50 PER CENT)

Drug	Patients (no.)	After Termination of Therapy for				
		16 Hours	40 Hours	64 Hours	88 Hours	112 Hours
Bishydroxycoumarin	23	0	4	25	63	80
Diphenadione	23	4	17	47	73	77
Phenindione	24	0	8	62	87	95
Warfarin	20	0	0	50	80	90

effect with all four drugs. (Table x.) At eighty-eight hours following the last dose in 87 per cent of the patients treated with phenindione, 80 per cent of the patients treated with warfarin, 73 per cent of the patients treated with diphenadione and 63 per cent of the patients treated with bishydroxycoumarin prothrombin activity had returned to normal level (over 50 per cent). The difference between these figures is not statistically significant.

Twelve patients were given vitamin K_1 oxide intravenously either because of bleeding or to permit the performance of a surgical procedure. In all cases prothrombin activity had returned to normal (over 50 per cent) within twenty-four hours. None of these patients were given further anticoagulants.

Complications. Hemorrhage was the most frequent complication encountered. Hematuria was present in eleven cases. It was not massive in any case and was usually managed by temporary withdrawal of the anticoagulant. Five episodes of gastrointestinal bleeding were characterized by melena and a drop in hemoglobin, three patients requiring transfusion of whole blood. Two patients died within a few days after a massive gastrointestinal hemorrhage. Both were in severe chronic congestive heart failure, receiving anticoagulants for recurrent pulmonary infarction. In neither case did the bleeding appear to be the immediate cause of death, but it may have helped to precipitate an already proximate death from heart disease. Three of the five patients had been receiving steroid therapy and may have bled from steroid-induced ulcer. Another major hemorrhage occurred in a patient with advanced rheumatic heart disease and recurrent pulmonary infarction who experienced massive hemoptysis, with a drop in hemoglobin from 10 to 7 gm. per 100 ml. In all, there were six major bleeding episodes, an incidence of 2 per cent, and seventeen minor episodes, an incidence of 6 per cent. (Table xi.) Of the twenty-three bleeding episodes, only four occurred when the prothrombin activity was below 10 per cent and nineteen when it was in the therapeutic range. We consider that bleeding is an extension of the pharmacologic

TABLE XI
COMPLICATIONS IN 287 CASES

Complication	Bishydroxycoumarin	Diphenadione	Phenindione	Warfarin	Total	
					No.	Per cent
Hemorrhage (major)						
Gastrointestinal	..	..	3	2	5	...
Hemoptysis	..	1	..	..	1	...
Total	..	1	3	2	6	2.0
Hemorrhage (minor)						
Hematuria	6	3	..	2	11	...
Cutaneous	2	..	..	..	2	...
Epistaxis	2	1	..	..	3	...
Gingival	1	..	..	..	1	...
Total	11	4	..	2	17	6.0
Fever, scarlatiniform rash, eosinophilia	..	..	1	..	1	...

effect of the drugs and not to be regarded as a toxic reaction. Since the four drugs which were studied have the same pharmacologic properties it does not seem reasonable to believe that one drug would induce bleeding more readily than another at a comparable level of prothrombin activity.

One patient had fever, scarlatiniform eruption and eosinophilia while receiving phenindione, with prompt remission following withdrawal of the drug. This was the only non-hemorrhagic complication encountered during this study which could be attributed to any of the four drugs. We have, however, seen two other severe reactions to phenindione at the Philadelphia Veterans Administration Hospital during the past four years. Both were characterized by agranulocytosis, fever and scarlatiniform eruption [*10*].

COMMENTS

Earlier studies have shown that the effect of a single large dose of an anticoagulant drug is fairly uniform in its initial prothrombin depressant effect from patient to patient although the duration of its effect is variable [*1*]. This can probably be attributed to differences in the rate of catabolism of the agent. It might therefore be anticipated that a single initial dose large enough to produce the desired prothrombinopenic effect would, by eliminating the variable rate of excretion of multiple smaller induction doses, result in more rapid and predictable attainment of therapeutic prothrombin levels. In the present study the use of the larger initial doses was accompanied by less variation in the size of the induction dose from patient to patient and by more rapid achievement of therapeutic prothrombin levels. By avoiding a prolonged induction period, and the resultant overlapping of the effects of induction and maintenance doses, earlier establishment of a stable maintenance dose is also facilitated. This tends to eliminate wide swings in prothrombin levels often observed in the early days of anticoagulant therapy.

The large doses are safe since of 134 patients only five had a transient depression of prothrombin activity to less than 10 per cent, and none of the five patients had any complications. A few patients complained of nausea but no vomiting after receiving large doses of dicumarol, but not after ingesting comparable doses of the other three drugs.

The onset of action of the initial dose of all four drugs was at approximately twelve hours. At sixteen hours depression of prothrombin

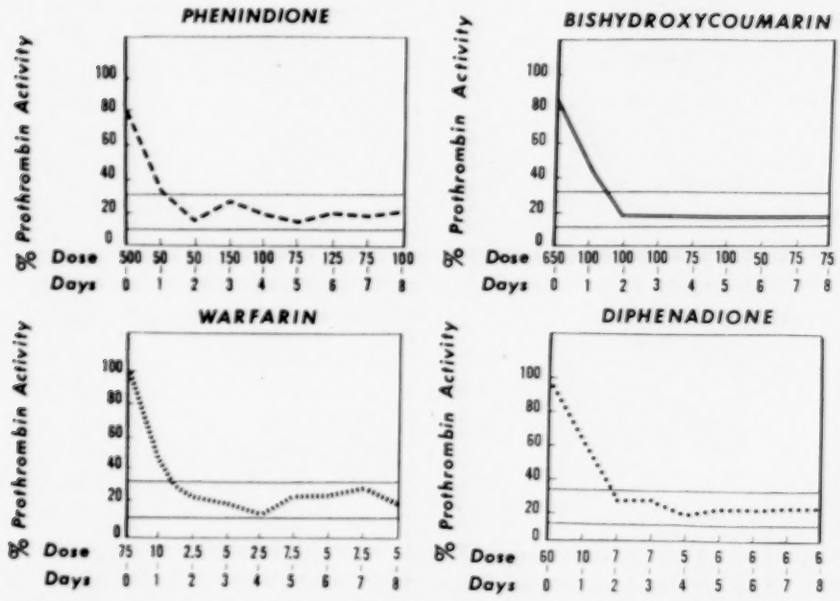


FIG. 1. Typical dosage and prothrombin activity during the initial eight days of therapy in a patient given each of the four anticoagulants.

activity was almost always demonstrable. The degree of this early depression did not, however, correlate well with the magnitude of the peak effect, which occurred at about forty hours. This means that although two patients with the same initial prothrombin activity may have prothrombin activities of 70 per cent and 40 per cent, respectively, sixteen hours after identical doses of the same drug, at forty hours the prothrombin activity of the first patient may have dropped to 16 per cent while that of the second may show only a small further drop to 28 per cent. The sixteen-hour prothrombin activity determination is therefore of little value in assessing further dosage requirements. It is useful only in picking up the occasional hypersensitive individual whose prothrombin activity has dropped rapidly to the therapeutic level. Accordingly, it has been our practice to give a maintenance dose on the second day to all patients except those whose prothrombin activity was in the therapeutic range at sixteen hours. The forty-hour prothrombin activity determination is important since it coincides with the peak effect of the drug. If it is at the upper limits or above the therapeutic range a larger subsequent dose is indicated. If it is at the lower limits of the therapeutic range a small dose should be given.

Table XII lists the induction program which we have found most useful for each drug. With phenindione, which is somewhat more rapid in onset of action and peak effect than the other three drugs, prothrombin activity in all twenty-five patients whose initial dose was over 350 mg. was in the therapeutic range at forty hours. Although this is significantly better than the results obtained with warfarin and bishydroxycoumarin, it is not significantly better than the results obtained with diphenadione, and it is doubtful that the difference among the drugs is sufficiently great to recommend one or the other as the drug of choice for induction therapy. Figure 1 illustrates the first eight days of therapy in a patient on each drug.

We have not had sufficient experience with patients whose initial prothrombin activity is less

TABLE XII
RECOMMENDED INITIAL DOSE

Drug	Dose with Control Prothrombin Activity of		
	80–100 Per cent	60–80 Per cent	50–60 Per cent
Bishydroxycoumarin	650 mg.	600 mg.	550 mg.
Diphenadione	60 mg.	55 mg.	50 mg.
Phenindione	500 mg.	450 mg.	400 mg.
Warfarin	75 mg.	70 mg.	60 mg.

than 50 per cent to suggest a dosage schedule for them. It should be emphasized that although we have had no bleeding complications in the patients who received the large loading doses, we do not suggest that a fixed program be followed to the exclusion of individual patient evaluation. For example, large initial doses should probably not be used in advanced chronic illness or diseases that would complicate anticoagulant therapy (i.e., liver disease).

Our data suggest that patients who received bishydroxycoumarin or diphenadione were more readily maintained within the therapeutic range than those who received warfarin or phenindione. (Tables III and IV.) We believe that this was the only important advantage of one drug over another than was demonstrated in this study.

The dosage requirement from day to day in the same patient varied less for bishydroxycoumarin and diphenadione than for phenindione and warfarin. The variation in maintenance dose from patient to patient was least with warfarin, probably because of the more complete absorption of this drug from the gastrointestinal tract. It is doubtful whether either of these is a clinically useful difference.

The return to normal prothrombin activity was slow following withdrawal of all four preparations. Phenindione appeared to be metabolized somewhat more rapidly than any of the other three drugs.

On the basis of our observations, none of the four drugs studied appears to have enough advantages over the others to be recommended as the prothrombinopenic agent of choice. This study has demonstrated that the majority of patients can be well controlled with the administration of any one of the four drugs. Daily prothrombin determinations are not essential for this control after a stable therapeutic level has been reached. The control achieved with prothrombin determinations three times a week compares favorably with that attained by others with daily determinations in studies with the same drugs.

None of the three newer drugs was better than bishydroxycoumarin, although diphenadione appeared to be as good. The chief disadvantage of bishydroxycoumarin has been the relatively long induction period. Using the larger initial dosage schedule this disadvantage has been reduced but not eliminated.

Advocates of phenindione have recommended that it be given twice daily for optimum control [9]. In extensive previous experience in our hospital with phenindione administered every eight hours and then every twelve hours no better control was obtained than with the single daily dose.

Warfarin has the advantage over the other three preparations in that it is available in stable parenteral form which can be used in patients who are unable to take the drug orally.

SUMMARY

Four prothrombinopenic anticoagulants were compared under controlled conditions in 287 patients over a period of fourteen months. Somewhat better control was achieved with bishydroxycoumarin and diphenadione than with phenindione and warfarin. The differences were statistically significant but not great. Satisfactory control was achieved in the majority of patients with all four drugs.

There was relatively wide variation in dosage requirements in the same patient from day to day and among patients receiving the same preparation. This variation was less with bishydroxycoumarin and diphenadione than with phenindione and warfarin, but the differences were not sufficient to be clinically useful.

An induction schedule which consisted of a large single loading dose followed by a small maintenance dose was found to be desirable and safe. Using such a program the prothrombin activity in the majority of patients (82 per cent) was brought into the therapeutic range within forty hours of the initial dose with all four drugs. This program also facilitated the early establishment of a stable maintenance dose.

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Comparison of Chlorambucil and Myleran® in Chronic Lymphocytic and Granulocytic Leukemia*

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Following the introduction of the nitrogen mustard compounds into cancer chemotherapy in 1946, an intensive effort was made to develop agents of greater therapeutic efficacy. More than 600 new compounds containing one or more active chloroethylamine groups attached to aliphatic, aromatic, sugar, amino acid, antimalarial and other carriers were synthesized and tested in screening programs. Chemical studies showed that different mustard derivatives reacted under mild conditions in aqueous solution, such as would prevail *in vivo*, to unite with important functional groups present in proteins and nucleic acids [*1–3*]. The chemical reactivity of various compounds generally paralleled their biologic activity. The latter included cytotoxic alterations, chromosome changes, mutations, carcinogenesis and inhibition of tumor growth.

To date about thirty different nitrogen mustard compounds have been given limited or extensive clinical study. The most important of these are perhaps the original methyl-bis(β-chloroethyl)amine (HN_2, Mustargen®) and triethylene thiophosphoramide (Thio-TEPA, TSPA) both of which must be administered parenterally. The first mustard derivative suitable for oral administration was triethylene melamine (TEM), now replaced in large part by chlorambucil (CB 1348, Leukeran®) which has greater chemical stability in the intestinal tract and solubility properties that favor absorption and regularity in dosage effect.

It now appears that most of the potent mustard derivatives have a basic chemical similarity and possibly the same mechanism of action. The most active compounds have two or more ethylene-imino rings in the native molecule, or have structures readily converted into such under physiologic conditions. By reactions involving a carbonium ion ($-CH_2^+$) one group attached to a carbon atom is displaced by another. While both ionized acid groups and sulfhydryl groups are likely centers for reaction, the esterification of ionized acid groups, especially in nucleic acids, may well account for the antitumor effects of these agents [*2*]. Proof that various mustard compounds differ in their fundamental oncolytic property has been most difficult to obtain since allowances must be made for variations in solubility, dosage, chemical reactivity, the necessity for different routes of administration and the like.

Another series of active compounds, with a different alkylating side chain, was discovered by

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Haddow and Timmis who undertook a line of investigation on the assumption that sulphonic acid and other esters might have biologic effects comparable to those of the nitrogen mustards if they were to unite, also, with some cellular constituent(s) via the ethane group (i.e., "alkylate") [*4*]. Among the chemicals they synthesized and studied only the sulphonic acid esters were active. Compounds with two $—OSO_2CH_3$ functional groups connected by a chain of four or five CH_2 groups effectively inhibited the growth of Walker carcinoma 256 and produced a selective neutropenia in the rat. Further study of the compound with four CH_2 groups, Myleran,® quickly showed it to be an effective agent in the treatment of chronic myeloid leukemia in man [*5–7*].

Elson compared the hematologic effects of Myleran with those of nitrogen mustard compounds and radiation in the rat and discovered important differences in hematopoietic response [*8,9*]. The main effect of single doses of Myleran® was to cause a steady fall in neutrophils to about 10 to 20 per cent of normal some ten to twelve days after treatment. With single doses of chlorambucil the greatest effect was on the lymphocytes which fell rapidly to a minimum in about four days and then gradually returned to normal in eighteen to twenty days. Both agents had to be given together to be truly "radiomimetic." There appeared to be no additive toxicity of the two drugs under these circumstances, and in fact the intense bone marrow regenerative activity which followed the initial short-term myeloid-depressing effect of chlorambucil actually protected against the more delayed Myleran effect. An effect similar to that of Myleran, on the bone marrow primarily, was also produced by the more soluble dimethyl Myleran compounds, 4-amino stilbene and carcinogenic hydrocarbons. The predominantly lymphoid hematopoietic effect of the nitrogen mustards was produced by several aromatic mustard compounds, TEM and butadiene di-epoxide.

The mechanism by which Myleran exerts its biologic action remains uncertain. It may function in ways other than by alkylation or it may merely be selectively concentrated in myeloid tissues [*9*].

In clinical usage Myleran has been employed largely in the therapy of chronic granulocytic leukemia and closely related myeloproliferative disorders [*10,11*]. The nitrogen mustard derivatives have been used most widely in the treatment of chronic lymphocytic leukemia and the malignant lymphomas. Few attempts have been made to compare the effect of dimethyl sulfonate Myleran compounds with those of the nitrogen mustards in man. Some patients with chronic lymphocytic leukemia, malignant lymphomas and bronchogenic carcinoma have apparently responded significantly to the administration of Myleran [*12–15*]. Since HN_2 and TEM are both fairly effective in the treatment of chronic granulocytic leukemia [*10,16*], some activity from chlorambucil in this disease would be expected, and has recently been reported [*17*].

These observations have led to doubt in some quarters that agents presumed to act by alkylation have any degree of tissue specificity, and even to some question whether or not there is much difference between the effects of the ethylene-imino and dimethyl sulfonate compounds [*13,14,17*]. The object of the present study was to compare more systematically and conclusively the effect of these two types of agents, using Myleran and chlorambucil, in patients with chronic granulocytic and chronic lymphocytic leukemia.

METHODS AND PROCEDURES

Selection of Cases. All patients available to the investigators in whom the diagnosis of chronic granulocytic or lymphocytic leukemia was established beyond doubt were considered for experimental chemotherapy. The contribution of completed cases from individual hospitals was as follows:

Alabama	11
Duke	10
Emory	21
Kansas	9
Mississippi	4
North Carolina	10
Medical College of Virginia	4
Washington University	13
Total number of patients	82

Patients with chronic lymphocytic leukemia admissible for study were required to have an absolute lymphocytosis of 15,000 per cu. mm. or more in the circulating blood on at least two separate occasions. Overt symptoms of disease, and palpable enlargement of the superficial lymph nodes or spleen were not requisites. Previously treated patients were included provided (1) their disease was uncontrolled or in relapse, and (2) that radiation, steroids, TEM or HN_2 had not been given during the preceding three months. Patients were excluded if their hemoglobin concentration consistently was below 7 gm. per cent, if the platelet count was below 50,000 per cu. mm.

due to bone marrow replacement with lymphocytes, or if the reaction to the Coombs' test was positive.

Patients with chronic granulocytic leukemia admissible for study were required to have a white blood cell count of 35,000 per cu. mm. or more, with characteristic granulocytic immaturity present on at least two separate occasions, and a bone marrow apparently normal or hypercellular with a predominance of granulocytic elements. Overt symptoms of disease, palpable splenomegaly, and increased bone tenderness were not requisites. Patients who had been treated previously were included provided (1) their disease was uncontrolled or in relapse, and (2) that radiation, TEM or HN_2, etc., had not been given during the preceding three months, unless the disease was obviously progressive or uncontrolled despite these measures. Patients with more than 10 per cent myeloblasts in the circulating blood and those with acute myeloblastic exacerbation of chronic disease were excluded.

Pre-trial Evaluation. During the pre-trial study the performance status of patients was evaluated according to criteria developed by Karnofsky, and the size of the lymph nodes, spleen, and liver, recorded on body surface maps and/or 6 foot chest roentgenograms. Patients were observed for periods long enough to document the persistence and range of hematologic abnormalities, changes in physical findings, and the like, before starting therapy. Physical and laboratory measurements on which therapeutic evaluations were to be based were made at least twice before treatment was begun.

All patients with the diseases under study were reported to the statistical center, whether they qualified for experimental therapy or not. If patients suitable for study were not admitted, specific reasons for their rejection were recorded to avoid bias in selection.

Choice of Agents. Upon completion of the pre-trial studies the therapeutic agent to be given to a particular individual was chosen at random. A series of numbered envelopes containing treatment cards was prepared by the biostatistician for each institution and for each disease entity. When a suitable patient was ready to begin treatment, the envelope with the lowest number was opened and the designated agent administered.

Administration of Drugs. Both chlorambucil and Myleran were administered with the intent to produce either (1) unequivocal evidence of chemotherapeutic effect using the optimal safe dose, or (2) depression of bone marrow function, as judged by a downward trend in the white blood cell and/or platelet count sufficient to indicate that the maximal tolerated amount had been given. Therapy was initiated with a single daily dose of 6 mg. of Myleran or 12 mg. of chlorambucil given in the morning at least thirty minutes before breakfast. After two to four weeks the respective doses were increased or decreased according to a uniform schedule designed to achieve the first or second objectives indicated as 1 or 2. Chemotherapy was continued in all instances for a full three months before evaluation of the effect of the agent was attempted.

Evaluation of Results. Each completed case was reviewed by all investigators jointly as to the acceptability of diagnosis, adequacy of the chemotherapeutic trial and results. Group evaluation was made without revealing which therapeutic agent had been used. Responses to therapy were classified as follows:

An *excellent response*, equivalent to the so-called "complete remission," was defined as the virtual disappearance of all evidence of disease. The performance status of the patient remained or became as good as if the disease were not present and definite, relevant symptoms were absent. The hemoglobin concentration, hematocrit and platelet count were required to be within the normal range. In chronic lymphocytic leukemia, enlarged lymph nodes and splenomegaly, if present, must have disappeared. The white cell count had to range between 5,000 to 15,000 per cu. mm., lymphocytes in the circulating blood could not be over 40 per cent and lymphocytes in the bone marrow not over 25 per cent. In chronic granulocytic leukemia, it was necessary that fever, splenic enlargement and bone tenderness had disappeared, that the white cell count was 5,000 to 15,000 per cu. mm., and that granulocytes less mature than non-segmented neutrophils be 5 per cent or less.

Good responses indicated a major gain in disease control but with definite evidence of disease persisting at the end of three months. The performance status remained normal or improved during therapy and symptoms of disease were absent or less severe. Objective measures of disease activity, leukocytosis, anemia, enlarged nodes, splenomegaly, and the like, showed at least 50 per cent improvement induced and maintained by therapy.

Fair responses indicated an unequivocal but smaller degree of therapeutic benefit than stipulated for a good response, with improvement of some 20 to 50 per cent in objective measures of disease activity. The performance status improved and serious symptoms of disease were relieved. In patients with anemia of moderate severity, the hemoglobin must have increased by at least 2 gm. per cent and the hematocrit by 5 per cent.

Questionable effect referred to a possible reduction in disease activity or benefit from chemotherapy meriting further study. Included in this category would be improvement in performance status and/or in symptomatology without objective physical or laboratory evidence of benefit; reduction in leukemic leukocytosis, node, tumor, or spleen size, but with unrelieved or increasingly severe anemia; the same changes occurring in patients to whom optimal chemotherapy could not be given due to impaired bone marrow function as a result either of their

disease or of previous therapy; apparent retardation in the rate of progression of a given disease.

No effect after adequate dose and duration of chemotherapy indicated (1) unaffected progression of the disease, or (2) continuously active disease with no improvement in performance status, relief of symptoms or change in objective indices of disease activity beyond the range of variation of successive measurements.

Untoward effects of chemotherapy on bone marrow function as reflected by changes in hemoglobin concentration, platelet count and number of granulocytes were graded separately as follows: (1) *Minor*. A drop in hemoglobin of 3 to 5 gm. per cent during therapy, platelets from normal to below 100,000 per cu. mm., and/or a fall in absolute granulocyte count from normal levels to less than 1,500 per cu. mm. (2) *Major*. A fall in hemoglobin level of 5 gm. per cent or more, platelet count from over 100,000 to below 50,000 per cu. mm., and/or in granulocytes below 750 per cu. mm. (3) *Fatal or near fatal* depression of bone marrow function, with counts below those already stipulated.

Statistical Methods. The data comparing the effects of the two drugs upon the degree of remission of the disease and untoward effects were classified into contingency tables and analyzed by χ^2 tests. When the expected numbers in any category of the table were too small, adequacy of numbers being as defined by Cochran [*18*], the extension of Fisher's exact test for 2×2 tables was used [*19*].

The data analyzed in respect to cell and platelet counts, hemoglobin concentration and performance status were the pre-trial and end-of-trial measurements. Analysis of covariance, which adjusts the end-of-trial measurement for the pre-trial measurement, is the most exact method of examining these data. In the present study random assignment of patients to the drugs resulted in approximate equality of the pre-trial means. One of the reasons for the use of covariance analysis, viz. the adjustment of the end-of-trial means for differences in the pre-trial means, was therefore not applicable. Covariance analysis is still the preferred method of analysis because variation of end-of-trial measurements within the two groups can be considerably reduced by allowing for the effect of the pre-trial measurement. For our purposes, however, a less precise method based upon the comparison of the difference between the pre-trial and end-of-trial measurement for each patient served as a satisfactory substitute. The over-all comparison was made by means of t tests. When the latter did not show a significant difference in drug effect, the results of the t tests were checked by the more precise covariance analysis. In the analysis of the data on lymphocytic leukemia this check agreed with the t test for all measurements on which both analyses were used. In the analysis of the data on granulocytic leukemia, t tests showed no significant differences in the effect of the two drugs on any blood component except the white cell count. Covariance analysis, however, showed a highly significant difference in the effect of the two drugs on total white blood cells and absolute granulocyte counts.

RESULTS OF EXPERIMENTAL CHEMOTHERAPY WITH CHLORAMBUCIL AND MYLERAN IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

Fifty patients were admitted to the study, twenty-five were treated with Myleran and twenty-five with chlorambucil. In ten instances the therapeutic trial was considered to be inadequate or inconclusive. Eight of these were in the group treated with Myleran and two were in the group treated with chlorambucil. The trial was rated as inconclusive in three patients because chlorambucil was substituted for Myleran after only four to six weeks of therapy. This was done once by mistake, once in a premature attempt to compare the two agents in sequence, and once in a patient in whom severe anemia and thrombocytopenia developed making it mandatory to change agents. The latter patient failed to respond, also, to the subsequent administration of chlorambucil and steroids. Two of the patients taking Myleran died, and two were lost to follow-up. In one a Salmonella bacteremia developed, the treatment of which made evaluation of the antileukemic therapy impossible. Of the patients taking chlorambucil, one died and one failed to return for follow-up.

The distribution of inadequate trials, eight in the group taking Myleran and only two among those taking chlorambucil, may accordingly have been due in part to progression of disease during chemotherapy and possibly to adverse effects of Myleran. The group of patients in whom the therapeutic trial was inadequate will be omitted from further consideration even though this will tend to prejudice the therapeutic evaluation in favor of Myleran.

Forty patients with chronic lymphocytic leukemia completed three months of experimental chemotherapy as planned. Data comparing the age, sex, duration of disease and types of previous therapy administered, if any, in the two groups of patients are summarized in Table 1. The pretreatment blood values were virtually the same. (Fig. 1.) Assigning the patients to the two drugs at random appeared to have successfully separated the patients into two comparable groups.

The therapeutic response of the two groups of

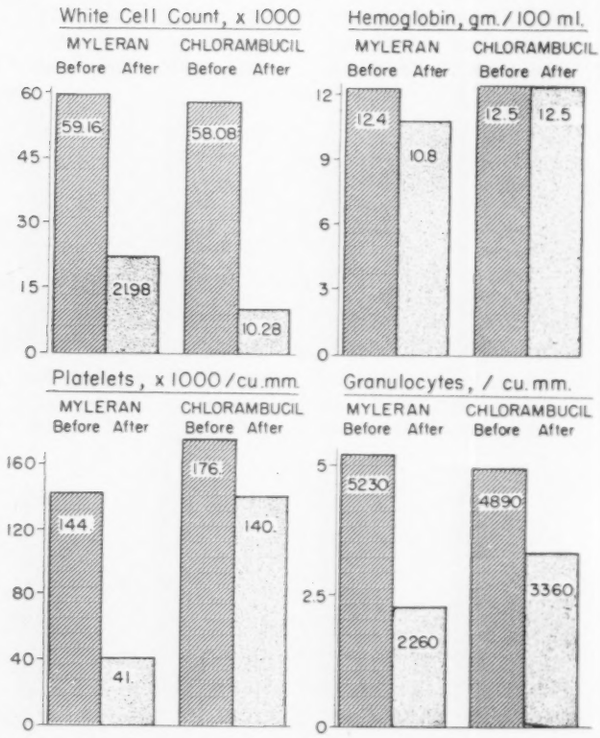


FIG. 1. Hematologic effects of chlorambucil and Myleran in chronic lymphocytic leukemia.

patients to Myleran and chlorambucil, as evaluated at the end of a trial period of three months, is summarized in Table II. With chlorambucil therapy fifteen of twenty-three patients (65 per cent) had good or excellent responses. None of the patients given Myleran responded to this degree. There were three fair responses to Myleran and two to chlorambucil. Questionable responses, referring mostly to a fall in white blood cell count without evidence of selective antileukemic effect otherwise, were observed in nine patients given Myleran and in six given chlorambucil. Most of these patients when followed up for longer periods of time during therapy with the same or different agents or steroids, still showed poor clinical and hematologic responses, indicating that the initial evaluation was approximately correct.

The difference in the response to the two drugs was highly significant. The probability of their having occurred by chance alone, assuming that the two agents are equally effective, is less than 1 per cent. One can predict with 95 per cent confidence that 54 to 88 per cent of patients with chronic lymphocytic leukemia, selected and treated as described, would have a fair or better response to chlorambucil, while only 5 to 42 per cent treated with Myleran would respond to this degree.

TABLE I
SUMMARY OF CLINICAL DATA PERTAINING TO PATIENTS WITH CHRONIC LEUKEMIA

Data	Lymphocytic Leukemia		Granulocytic Leukemia	
	Myleran	Chlorambucil	Myleran	Chlorambucil
No. of patients	17	23	21	21
Age (yr.):				
Range	43–81	44–85	25–79	20–76
Mean	61.4	59.5	48.1	47.1
Sex:				
Male	15	17	6	11
Female	2	5	15	10
Duration of disease, months:				
Range	0(?)–84	0(?)–88	0(?)–60	0(?)–60
Mean	28.5	23.9	13.1	10.5
Previous therapy:				
P^{32}	2	3	3	0
X-ray	3	5	0	1
Chemotherapy	7	5	6	5
None	8	14	14	14

TABLE II
SUMMARY OF THE THERAPEUTIC RESPONSE OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TO CHLORAMBUCIL AND MYLERAN

Response	Myleran	Chlorambucil
Excellent	0	3 (13%)
Good	0	12 (52%)
Fair	3 (18%)	2 (9%)
Questionable	9 (53%)	6 (26%)
None	5 (29%)	0
Total no. patients	17	23

The hematologic status of the two groups before and at the end of experimental chemotherapy is compared in Figure 1. The mean hemoglobin concentration of each group and the geometric mean of the platelet, white blood cell and absolute granulocyte counts are charted.*

The mean white blood cell count, a major index of therapeutic response, fell significantly from 58,000 to 10,280 per cu. mm. in the group of patients given chlorambucil and from 59,160 to 22,000 per cu. mm. in those treated with Myleran. With the latter agent adverse effects

* The geometric mean, the antilogarithm of the average of the logarithms, was used to compensate for extreme variations in counts plus the fact that accuracy of the counts decreased as they became higher.

on platelet and granulocyte counts (*v. seq.*) made it inadvisable to give enough of the chemical to lower the total white blood cell count as much as appeared to be safe with chlorambucil.

The mean hemoglobin concentration and platelet count in patients treated with chlorambucil showed no significant change during the course of therapy. The mean absolute granulocyte count fell from 4,890 to 3,360 per cu. mm.

In the group of patients treated with Myleran there was a highly significant fall in mean hemoglobin concentration, 1.6 gm. per cent, and in the platelet count, 104,000 per cu. mm. The absolute granulocyte count fell from 5,230 to 2,260 per cu. mm. despite less depression of the total white blood cell count with Myleran than with chlorambucil.

The performance status of patients taking Myleran dropped slightly, from an average rating of 88 to 85, while that of patients taking chlorambucil improved from 90 to 94.

The untoward effects of the two agents on bone marrow function during the course of chemotherapy, graded as outlined previously, are summarized in Table III. Both agents appeared to be capable of reducing to some extent the hemoglobin concentration, platelet and granulocyte counts. Thrombocytopenia was the most serious adverse effect of Myleran. The difference between the two drugs in this regard was highly significant. The indications are that Myleran given in the doses used in this study will produce thrombocytopenia in 66 to 98 per cent of all patients with chronic lymphocytic leukemia while the incidence with chlorambucil would be 22 to 62 per cent. The incidence of major and dangerous depressions of the platelet count with Myleran was more than four times that with chlorambucil. There was some suggestion that Myleran also depresses the hemoglobin concentration and granulocyte count more than chlorambucil, but the data are not such that this is confirmed statistically. A real difference in the drugs in this regard might have been obscured by the relatively small number of patients studied.

TABLE III
UNTOWARD EFFECTS OF MYLERAN AND CHLORAMBUCIL ON BONE MARROW FUNCTION IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

	None	Minor	Major	Dangerous
Hemoglobin				
Chlorambucil	21 (91%)	1 (4.5%)	1 (4.5%)	0
Myleran	12 (71%)	3 (18%)	2 (12%)	0
Platelets				
Chlorambucil	13 (57%)	7 (30%)	3 (13%)	0
Myleran	2 (12%)	4 (24%)	8 (47%)	3 (18%)
Granulocytes				
Chlorambucil	15 (65%)	5 (22%)	3 (13%)	0
Myleran	8 (47%)	5 (35%)	3 (18%)	0

RESULTS OF EXPERIMENTAL CHEMOTHERAPY IN PATIENTS WITH CHRONIC GRANULOCYTIC LEUKEMIA

Forty-five patients with chronic granulocytic leukemia were admitted to the study. The random choice of agents resulted in the administration of chlorambucil to twenty-four patients and Myleran to twenty-one. The effect of the latter agent was subsequently studied also in five patients who had been given chlorambucil initially.

The chemotherapeutic trial was rated as inconclusive in three of the patients started on chlorambucil therapy. One died of unknown cause on the day treatment was begun. In another an acute leukemic exacerbation developed after one month of therapy and the patient died four weeks later. The third patient refused to continue taking chlorambucil since each dose seemed to produce nausea.

Forty-two patients completed the course of experimental therapy as planned. The age, sex, duration of disease, the number previously treated and untreated in both groups appeared to be comparable. (Table I.) The geometric means of the total white cell, platelet and granulocyte counts were slightly higher in those given chlorambucil, suggesting that the basic disease might have been somewhat more severe in this group. (Fig. 2.)

The difference in response to the two drugs as evaluated at the end of three months was highly significant. All the patients given Myleran had excellent or good responses. (Table IV.) Only twelve of the twenty-one patients given chlorambucil had a comparable degree of improvement, but in only one was the response ques-

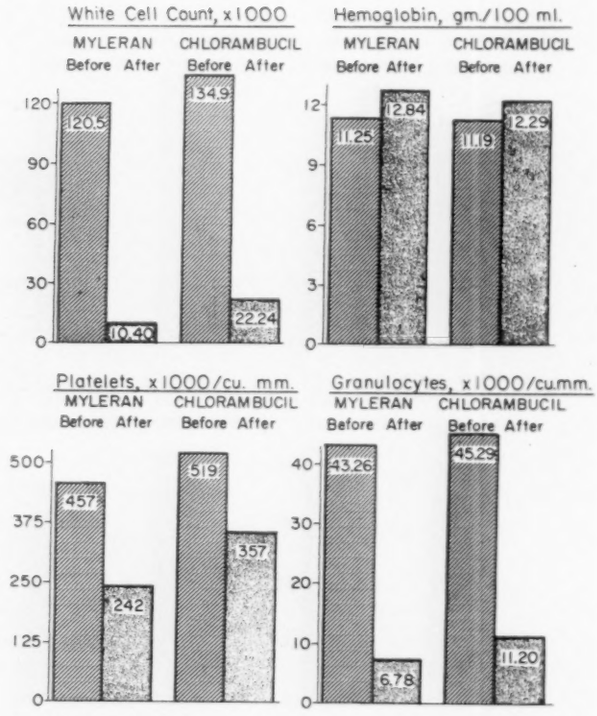


FIG. 2. Hematologic effects of chlorambucil and Myleran in chronic granulocytic leukemia.

tionable. One can predict with 95 per cent confidence that 87 to 100 per cent of the patients with chronic granulocytic leukemia, selected and treated as described, would have excellent or good responses to Myleran, and that only 34 to 79 per cent treated with chlorambucil would respond this well.

The hematologic status of the two groups before and at the end of experimental chemotherapy is compared in Figure 2. The mean hemoglobin concentration in both groups before treatment was virtually the same and during therapy it increased by about 1 gm. per cent. During the period of chemotherapy, the mean white blood cell count fell from 120,500 to 10,400 per cu. mm. in the patients given Myleran, and from 134,900 to 22,240 per cu. mm. in those given chlorambucil. The platelet and absolute granulocyte counts were depressed less by chlorambucil than by Myleran. While untoward effects from either agent were insignificant, Myleran had a definite tendency to lower the platelet count.

Larger doses of chlorambucil than those administered could have been given. This or a longer period of treatment might have made the final results of therapy more nearly equal. The only statistically significant difference in hematologic effects of the two chemicals in this study pertained to the total white blood cell and absolute granulocyte counts.

Some patients alleged that they felt better while taking Myleran than while taking chlorambucil. The performance status of both groups improved slightly during therapy, however.

Five of the patients given chlorambucil initially were allowed to have a relapse and then were treated with Myleran. The response of individual patients to the two agents given in this sequence was as follows:

TABLE IV
SUMMARY OF THE THERAPEUTIC RESPONSE OF PATIENTS WITH CHRONIC GRANULOCYTIC LEUKEMIA TO CHLORAMBUCIL AND MYLERAN

Response	Myleran	Chlorambucil
Excellent	8 (38%)	2 (9.6%)
Good	13 (62%)	10 (48%)
Fair	0	8 (38%)
Questionable	0	1 (4.8%)
Total no. patients	21	21

Patient	Initial Response to Chlorambucil	Subsequent Response to Myleran
1	Excellent	Good
2	Good	Good
3	Good	Good
4	Fair	Good
5	Fair	Good

COMMENTS

All the patients selected for study had disease showing objective evidence of activity and none had been given recent therapy that might alter its course. After a period of pre-trial observation, during which possible fluctuations in clinical status, physical and laboratory measurements were studied, the therapeutic agent to be administered was chosen at random. Each compound was given according to a schedule calculated to produce either (1) an unequivocal effect on the manifestations of disease activity, or (2) a depression of bone marrow function sufficient to indicate that the maxi-

mal tolerated dose had been given. The results of chemotherapy after an arbitrary period of three months were evaluated by the group of investigators jointly without knowledge of which agent had been given.

Fifty of the eighty-two patients studied had had no previous treatment for leukemia. In those who had been treated, there was no evidence of delayed response or complication discernible at the time experimental chemotherapy was begun. Analysis of the age, sex, duration of disease, prior therapy or lack of it, and hematologic data before therapy indicated that the patients with each type of leukemia had been divided into two comparable groups by the procedure used for the assignment of drugs.

In twenty-three patients with chronic lymphocytic leukemia, chlorambucil produced good or excellent responses in fifteen (65 per cent). None of the seventeen patients treated with Myleran responded this well and in fifteen thrombocytopenia developed with the platelet count dropping below 100,000 per cu. mm. In only ten (43 per cent) of twenty-three patients treated with chlorambucil did thrombocytopenia develop. Serious depressions of platelet count were produced four times as often by Myleran as by chlorambucil.

The platelet-depressing effect of Myleran, and to a lesser degree its effect on the granulocytes, is serious enough to prohibit its therapeutic use in chronic lymphocytic leukemia. The almost uniform involvement of the bone marrow in this disease by lymphocytic infiltration or proliferation may predispose to this untoward effect [*16*].

Twenty-one patients with chronic granulocytic leukemia were treated with Myleran and twenty-one with chlorambucil. All of those given Myleran had good or excellent responses. Only twelve of twenty-one patients treated with chlorambucil responded this well, but in only one instance was the response questionable. Untoward effects of significance were not observed with either agent in this disease.

It is of considerable interest and importance to note that the hematopoietic effects of chlorambucil and Myleran in the chronic leukemias of man are those that would have been predicted from the experimental studies in the rat. Elson demonstrated that single doses of chlorambucil, and of other nitrogen mustard compounds, affected the lymphoid tissues in rats primarily, while Myleran acted predominantly on the bone marrow [*9*]. Chlorambucil has produced lymphopenia, and less regularly some degree of thrombocytopenia, in patients with a normal bone marrow [*20*]. There is every indication that Myleran affects the normal bone marrow elements in man to a greater degree than the lymphoid tissue, just as it does in the rat. The present study indicates that the abnormally proliferating cells in chronic lymphocytic and granulocytic leukemia retain the basic difference in susceptibility to the two types of alkylating agents shown by the parent tissues.

It was somewhat disconcerting to find that about one-third of all patients with chronic lymphocytic leukemia responded poorly or not at all to chlorambucil therapy. While the adrenocortical hormones provide most useful additional antileukemic control in this group of patients, more effective chemicals than chlorambucil might be discovered if chloroethylamine compounds could be developed which have less effect on the bone marrow.

In chronic granulocytic leukemia, chlorambucil affects the bone marrow sufficiently at a relatively high dose level to be a fairly good therapeutic agent. It appears to be less efficient than Myleran in suppressing excessive platelet proliferation. On occasion this may be a useful attribute. Relapses occur quickly when chlorambucil therapy is suspended, but the agent may be safer to use on this account since long lasting depressions of bone marrow function are less likely to occur than with Myleran. The possible influence of different agents on progressive increase in severity of the disease and the ultimate development of acute exacerbations, the most important unsolved clinical problem, has not been studied.

Chlorambucil and Myleran appear to have distinctly different qualitative effects on the lymphoid and myeloid tissues in man. Efforts in synthesizing new nitrogen mustard compounds have emphasized the attachment of different rings, radicles and side chains to chloroethylamine groups. While these impart most useful and important pharmacologic properties to the oncolytic moieties, the search for new alkylating groups should not be neglected. Advances in this direction could lead to the development of new classes of agents with different tissue specificities than those presently available.

SUMMARY AND CONCLUSIONS

The effects of chlorambucil and Myleran therapy have been studied in parallel in forty

patients with chronic lymphocytic leukemia and in forty-two patients with chronic granulocytic leukemia.

In chronic lymphocytic leukemia, chlorambucil produced good or excellent therapeutic responses in fifteen of twenty-three patients (65 per cent). None of seventeen patients treated with Myleran responded this well and in fifteen thrombocytopenia developed due to adverse effects on the bone marrow.

In chronic granulocytic leukemia, Myleran produced good or excellent therapeutic responses in all twenty-one patients treated. Only twelve of twenty-one patients given chlorambucil had comparable responses.

Chlorambucil and Myleran appear to have relatively specific growth inhibitory effects on the lymphoid and myeloid tissues, respectively. This finding should encourage further search for new alkylating groups with the possibility of discovering oncolytic agents with different tissue specificities than those presently available.

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Pseudoxanthoma Elasticum*

A Systemic Disorder

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PSEUDOXANTHOMA elasticum is an easily recognizable clinical and morphological entity which may be associated with ophthalmologic, gastrointestinal and peripheral vascular lesions of clinical importance. The occurrence of angioid streaks of the retina in association with pseudoxanthoma elasticum constitutes the Grönblad-Strandberg syndrome, in which progressive retinal changes may lead to serious impairment of vision and even to blindness. Gastrointestinal hemorrhage may result from vascular changes in the mesentery with secondary mucosal involvement at any level of the gastrointestinal tract. Peripheral vascular lesions in the extremities may lead to weak pulses, abnormal oscillometric findings and intravascular calcifications. Although the eye and skin findings have for years attracted the attention of ophthalmologists and dermatologists, the systemic nature of the disorder has not received sufficient attention among internists, and many patients with this disorder have undoubtedly been unrecognized.

CASE REPORTS

CASE 1. A. H. M., a forty-seven year old married woman, was referred to Emory University Clinic on February 10, 1958, because of recurring episodes of diarrhea and abdominal pain. She stated that in March 1953 acute bloody diarrhea developed, with more than twelve bowel movements in a twenty-four-hour period, associated with moderately severe cramping abdominal pain. The acute symptoms subsided within three days but she continued to have loose stools once or twice a day for the next two weeks. Following this her stools returned to normal for six months, when there again developed a less severe episode of diarrhea associated with the passage of small amounts of blood lasting for about a week. She has since had recurrent episodes of diarrhea, with small amounts of blood and large amounts of mucus, once or twice a year, lasting about two weeks at each recurrence. X-ray film studies of her colon, upper gastrointestinal tract and gallbladder were obtained in 1953 and again in 1955, and were interpreted as revealing no abnormalities. The most recent episode of diarrhea was in December 1957 and was associated with cramping pains in the right upper quadrant of the abdomen. The diarrhea again lasted about two weeks and although she did not notice blood at this time she felt very weak. She was not having diarrhea at the time of her admission to the Clinic.

For the past year and a half she had been aware of skin lesions on the back of her neck which became red and tender in the summertime but gradually lost their inflammatory appearance during cold weather and involved a smaller area than previously. When the inflammatory phase subsided small "bumps" remained on the back of her neck which were slightly sensitive. She was aware of no other skin lesions. She had no visual difficulty. She denied any history of epistaxis, bleeding gums or purpura. However, she had experienced severe menometrorrhagia at the age of thirty-two and subsequently until hysterectomy was performed in 1942. She was told that she had ulceration of her cervix and ulcers in her womb.

There was no history of bleeding tendencies in the family. She denied any knowledge of skin disorders or visual troubles in any of her relatives. She had no knowledge of symptoms of coronary artery disease among any of her relatives with the exception of her seventy year old father.

Physical examination revealed a well developed and well nourished woman in no acute distress. The blood pressure was 140/100 mm. Hg in the arms and 165/105 mm. Hg in the legs. Examination of the posterolateral aspects of her neck revealed multiple tiny, yellowish, plaque-like, somewhat raised lesions immediately beneath the dermis. These plaques were especially prominent when the skin was pulled taut. There was no associated erythema or ulceration. Suggestive lesions of a similar character were also noted in the axillas and in the antecubital spaces bilaterally. There was no lymphadenopathy. Examination of the eyes revealed normal extraocular movements and pulmonary reactions. Retinal examination disclosed

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angioid streaks bilaterally, especially along the upper edge of both nerve heads. In addition there were prepapillary membranes which caused both discs to be blurred. There was moderate choroidal sclerosis around the discs and only mild retinal arteriosclerosis. There were no retinal hemorrhages and macular degeneration was not present. The thyroid gland was moderately enlarged. Peripheral pulses were normally palpable throughout. The heart was normal in size, shape and rhythm. The heart sounds were of good quality, and no murmurs were heard. Abdominal examination revealed mild tenderness in the right and left lower quadrant. Two linear scars of hysterectomy and appendectomy were noted. Pelvic and rectal examinations were normal. The neurological examination was within normal limits. Sigmoidoscopic examination revealed normal mucosa to 20 cm.

The hemoglobin was 12.9 gm. per cent; white blood cell count, 5,850 per cu. mm. with a normal differential. The erythrocyte sedimentation rate was 35 mm. (Westergren). Random urinalysis revealed a pH of 5, specific gravity 1.001, no albumin or sugar; the microscopic examination was normal. A serologic test for syphilis was negative. A glucose tolerance test was normal. X-ray film studies of the extremities, skull and chest showed a normal outline of the bones of the upper and lower extremities and no soft tissue calcifications were noted. The roentgenogram of the chest was within normal limits and the skull showed no radiographic abnormalities. Oscillometric and skin temperature determinations were made on all four extremities, and these were normal.

Biopsy of the skin lesion on the back of the neck revealed the changes of pseudoxanthoma elasticum.

Comment: This patient had experienced unexplained gastrointestinal bleeding at recurrent intervals for five years. Examination revealed the skin changes of pseudoxanthoma elasticum and examination of her retina revealed angioid streaks. It is possible that her gastrointestinal bleeding episodes represent intestinal mucosal changes secondary to involvement of the mesenteric vessels with this disease.

Case II. M. W., GMH No. 187679, a sixty-one year old Negro woman was first admitted to Grady Memorial Hospital on July 30, 1956, with the chief complaint of pain in the chest. She gave a six-month history of migratory polyarthritis with swelling, heat, pain, tenderness and fever up to 104°F. and profuse sweating, for which she had been treated with cortisone tablets. Eight days prior to admission pain in the left anterior side of the chest developed, with radiation to the left shoulder. The pain was pleuritic and progressively severe. She reported a 40- to 50-pound weight loss during the six weeks prior to admission.

Past history revealed that fifteen years prior to admission a uterine fibroid had been removed. Fourteen years previously she had undergone surgery for "locked bowel." Ten years previously she had had sudden bilateral blindness, with return of her sight in two days. She had known of having high blood pressure for at least two years.

Physical examination on admission revealed a blood pressure of 106/60 mm. Hg; pulse, 92; respirations, 32 and shallow; temperature, 99.2°F. Indications of chest pain were noted. There were no hot, swollen or painful joints. The skin was not thought to be abnormal. Examination of the chest revealed dullness to percussion up to D9 on the right side and D8 on the left side, with moist rales only in the areas of dullness. Examination of the fundi revealed that "at one disc diameter lateral to the left disc is a gray depression with irregular border."

The hemoglobin varied from 10.2 to 12.4 gm. per cent; hematocrit, 33 to 42 per cent. The urine had a specific gravity of 1.030 to 1.012; protein, absent to 2 plus; an occasional white blood cell was present. The erythrocyte sedimentation rate ranged from 53 to 36 mm. (Westergren). The white blood cell count ranged from 3,000 to 7,860 per cu. mm. A test for syphilis was negative. Direct serum bilirubin was 0.5 to 0.1; total bilirubin, 0.5 mg. to 1.3 mg. per cent. The blood urea nitrogen was 14 and 18 mg. per cent. The serum uric acid was 2.9 mg. per cent, total serum protein, 5.2 to 7.5 gm. per cent with albumin 2.1 to 2.3 gm. per cent. The thymol turbidity was 5.5 and 6 units, and the cephalin flocculation reaction was 1- to 2-plus. Results of a Coombs' test were negative. Results of L.E. cell tests were negative on eight occasions. Gastric washings for smear and culture were negative for acid-fast bacilli. A C-reactive protein test was 1 plus. Serum electrophoresis twice revealed an increase in the gamma globulins. Cultures of blood and pleural fluid were negative, as was guinea pig inoculation. Stains of the pleural fluid were negative for bacteria. Four thoracenteses yielded a red-brown fluid with 13,000 to 27,000 red cells and 2,000 to 14,000 white blood cells per cu. mm., with 85 per cent segmented forms on the first tap and 96 per cent mononuclears on subsequent taps. The protein of the pleural fluid was 5.5 to 6.3 gm. per cent. A biopsy of the right supraclavicular node yielded only a hyperplastic lymph node. A pleural biopsy showed no abnormalities. A P.P.D. skin test was positive for tuberculosis. Electrocardiogram on August 20, 1956, showed abnormal repolarization forces, with T lowered in V-5 and 6, L-2, 3.

No etiological diagnosis was established. The patient was discharged on October 19, 1956. She continued to take digitalis and was followed up in the outpatient clinic.

She was readmitted on January 25, 1957, for reevaluation. The patient continued to have dyspnea, polyarthritis and symptoms of pericarditis. Physical examination revealed a temperature of 100.4°F., pulse 80, blood pressure 140/90 mm. Hg, respirations

30. This time small yellowish papular lesions were noted in the anterolateral areas of the neck and axillas and in the popliteal areas. Large lymph nodes were present in the axillary and inguinal areas. Funduscopic examinations were thought to show classical angioid streaks and "retinitis pigmentosa." Pleural effusion was again present bilaterally. Examination of the heart revealed some enlargement. The rhythm was regular with clear heart sounds; P2 was greater than A2. There was a grade 2 aortic systolic murmur. A questionable pericardial friction rub was noted. The liver edge was palpable 4 fingerbreadths. Pelvic examination revealed considerable tenderness and a mucopurulent discharge. Arthritic changes were now noted in the small joints.

The specific gravity of the urine fluctuated between 1.010 and 1.020, with albumin ranging from 0 to 2 plus. Microscopic examination revealed 15 to 30 red cells and 10 to 15 white blood cells per high power field. The hemoglobin was 9.1 to 10.3 gm. per cent. The erythrocyte sedimentation rate was 35 mm. (Westergren). The white blood cell count ranged from 8,150 to 9,440 per cu. mm., with a normal differential. Six blood urea determinations ranged from 14 to 58 mg. per cent. Thoracentesis yielded pleural fluid which was straw-colored, with a specific gravity of 1.015 and 300 mononuclear cells per cu. mm. The venous pressure was 110 mm. of saline solution at the antecubital fossa. The circulation time was sixteen seconds arm to tongue. Several L.E. preparations were again negative. Results of a phenolsulfonphthalein test were normal.

A biopsy specimen of the skin revealed the changes of pseudoxanthoma elasticum. Ophthalmologists confirmed the existence of angioid streaks. Roentgenograms showed only vascular calcifications in the pelvic region.

The patient was given salicylate and for a time improved. However, with the development of hematuria and an elevation of the blood urea nitrogen she was given cortisone, with some improvement. Once when salicylate was stopped there was a flare-up of her polyarthritis. She was discharged on March 6, 1957, with the diagnosis of Grönblad-Strandberg syndrome. It was suspected that she had lupus erythematosus in addition, despite the negative L.E. cell tests.

The patient was followed up at monthly intervals in the outpatient department. Repeat roentgenograms of the chest showed clearing of the pleural effusion and a reduction in the size of the heart shadow, suggesting that some pericardial effusion had been present. She continued to have pain in the joints but her weight remained stable at about 137 pounds. (Prior to her illness she had weighed 190 pounds). She had several episodes of severe epistaxis. The cortisone was discontinued on August 31, 1957, without any striking change in her symptomatology.

The patient's third admission was on January 8, 1958. She complained of profound weakness and was found to have a hemoglobin of 3.8 gm. per cent. Physical examination revealed a pulse rate of 68, respirations 20, and blood pressure 190/90 mm. Hg. She appeared chronically ill. The skin was noted to have thickened; there were deeply pigmented, hard, raised areas in the axillas, popliteal areas, under the breasts and about the waist. These areas were noted to be tender. The other physical findings were essentially as before. Laboratory studies revealed the presence of anemia, a normal white blood cell and differential count; blood urea nitrogen, 90 mg. per cent; serum potassium, 7.1 mEq./L.; and CO_2, 12.5 mEq./L. The urine contained 20 red blood cells per high power field. She was given a transfusion of 2 units of packed red cells, bringing her hemoglobin up to 10.2 gm. per cent. Her blood pressure rose to 210/100 mm. Hg and her blood urea nitrogen to 140 mg. per cent. (Electrocardiogram on January 21, 1958, showed left ventricular hypertrophy). Her course was steadily downhill; she became disoriented and died quietly on January 28, 1958. Request for an autopsy was declined.

Case III. (C. L. W., GMH No. 287,498). A fifty-four year old married Negro woman was admitted on November 27, 1956, to Grady Hospital for investigation of chronic anemia. She had first been seen as an outpatient on July 19, 1955, complaining of swelling and redness in the right wrist. An x-ray film of the wrist taken at that time revealed a striking calcification of the radial and ulnar arteries and this was correlated with the physical finding of bony hard nodularity of these same vessels with almost absent pulsations in them. She was seen several times rather briefly complaining of recurrence of pain in the wrist for which she was given aspirin. On February 8, 1956, she was again seen in the medical clinic and found to have a hemoglobin of 6.6 gm. per cent with a hematocrit of 26 per cent, red cell count of 1.89 million per cu. mm., and serologic test for syphilis positive 1:1. A chest roentgenogram showed moderate enlargement of the heart with emphysema and pulmonary fibrosis.

Apparently she had been well until 1954 when she commenced having exertional dyspnea and substernal tightness on exertion. Polydipsia and polyuria developed at this time, with nocturia twelve to fifteen times nightly. These symptoms progressed to the point where she was forced to cease her work as a maid. With worsening of her symptoms she began to have migratory polyarthritis especially involving the wrists, ankles and knees. She had had difficulty seeing, associated with a "dot" in the vision of her right eye. The history indicated that her diet was extremely poor and efforts were made to secure financial help from the social service department.

Little was known of the family history. The patient had had four pregnancies, all ending in abortions.

Physical examination at the time of admission revealed a pulse of 64; blood pressure, 110/82 mm. Hg; weight, 134 pounds. Her height was more than 6 feet, and she had a striking appearance with long, gracile limbs and distinct arachnodactyly: the typical habitus of Marfan's syndrome. A cleft palate was noted, as was a bilateral Harrison's groove. The heart did not appear enlarged but a grade 2 to 3 systolic murmur was heard parasternally in the third to the fifth interspaces on the left side, without radiation. Examination of the eyes revealed an arcus senilis bilaterally. One observer thought that there was something unusual about the eye grounds but did not describe his findings. Rectal examination revealed prominent hemorrhoids. Until the time of admission, the patient's anemia was treated with an oral iron preparation, without improvement. Her stools were persistently 2- to 4-plus guaiac-positive. The urine contained varying numbers of white blood cells and occasional albuminuria. A Bence Jones protein test was negative. The serum total protein was 8.4 gm. per cent with albumin 3.3 and globulin 5.1 gm. per 100 cc. The serum phosphorus was 2.8; calcium, 11.5; and serum uric acid, 6 mg. per cent.

In the hospital she was seen by several consultants, one of whom (Dr. Albert A. Brust) noted that in addition to a Marfan's habitus the patient had classical angioid streaks in the retina. This observation, together with a history of gastrointestinal bleeding and the finding of calcification of the arteries of the arm suggested the possibility of a "mixed" picture of Marfan's syndrome and pseudoxanthoma elasticum. The discharge diagnoses were (1) congenital defect of elastic tissue giving mixed picture of Marfan's syndrome and pseudoxanthoma elasticum, (2) secondary anemia, (3) rheumatoid arthritis.

The patient was admitted for a second time on May 9, 1957, with cough, pleuritis in the left side of the chest with pain and fever, and an infiltration in the right cardiophrenic angle as seen on x-ray examination. A urinary tract infection was also noted and was treated with penicillin and sulfathiazole. The response was uneventful. While in the hospital she was seen by Dr. Victor A. McKusick of Johns Hopkins Hospital, who agreed with the combined diagnoses of Marfan's syndrome and pseudoxanthoma elasticum despite the absence of skin lesions and of subluxation of the lens. Biopsy specimen of the skin was normal. An electrocardiogram taken on May 10, 1957, revealed a wide QRS-T angle. The patient was discharged on May 24, 1957, to be followed up as an outpatient. On September 18, 1957, she was brought to the Emergency Clinic, dead on arrival, and no history was obtainable from other sources.

Comment: This case offers the interesting possibility of bridging the gap between the diseases of connective tissue on the one hand and the congenital mesodermal dystrophies on the other. A well documented migratory polyarthritis was present in addition to Marfan's syndrome and pseudoxanthoma elasticum.

COMMENTS

Pseudoxanthoma elasticum first attracted notice as a skin disorder in France. Balzer [*1*] described the first autopsy case in a tuberculous patient in 1884. He thought the disorder belonged to the xanthomatoses. A second case attracted the interest of Chauffard [*7*] in 1889. Darier [*11*] obtained a biopsy specimen of this patient's skin and, noting that the degenerating tissue stained like elastin, gave the disorder its present name. His account in 1896 is now a classic in dermatologic literature [*55*]. This patient suffered from multiple gastrointestinal hemorrhages between the ages of twenty-four and thirty-three. In 1903 amblyopia developed in the patient. Because of the wide interest in the case, Hallopeau and Laffitte [*27*] reported the ocular findings. Although no mention was made of angioid streaks, note was taken of a chorioretinitis involving the macula and the suggestion was made that a systemic illness was involved.

Contemporaneous with the discovery of pseudoxanthoma elasticum by the dermatologists, ophthalmologists took an interest in another disorder which was to be linked to the skin disease many years later. Doyne [*14*] in 1889 gave the first description of angioid streaks and Knapp [*33*] in 1892 gave the finding its descriptive name. In the ensuing years a lively controversy arose as to the origin and nature of these streaks. The most popular theory was that of hemorrhage. Kofler's [*34*] suggestion in 1917 that the lesion represented a rupture in the elastic membrane was given little support. The discovery of the association of the eye with the skin disorder was an important step in the study of this disease. Carlborg's [*6*] account of this event is most interesting. In 1929 Dr. Esther Grönblad, an ophthalmologist in Stockholm, Sweden, became interested in a patient with angioid streaks. She referred the patient to Dr. Arthur Engel, internist, for a medical work-up. He took note of a skin disorder with which he was not familiar. The patient was then referred to Dr. James Strandberg, dermatologist, who recognized the skin lesion as pseudoxanthoma elasticum. Grönblad [*23*] and Strandberg [*57*] then collaborated in reporting a series of cases with this combination of findings and

the syndrome came to bear their names. In the ensuing decade they were able to accumulate nearly thirty cases in Sweden alone [*6,22*]. The association has since been reported from all over the world and now numbers more than 200 cases. In 1941 Scholz [*51*] reviewed 188 cases of angioid streaks reported in the literature and noted that fifty-nine patients had been found to have pseudoxanthoma elasticum. Sandbacka-Holström [*50*] reviewed 100 cases of pseudoxanthoma elasticum and found that 87 per cent of the patients were reported as having angioid streaks.

McKusick [*43*] has translated Chauffard's detailed description of the skin lesions, and other excellent accounts are to be found [*16,32*]. The disorder has ranged from a barely perceptible roughening in a small area on the neck, as in one of our cases, to a striking generalized bodily involvement with marked cutis laxa and wrinkling, as shown in a photograph by Shaffer et al. [*53*]. At times, biopsy of normal-looking skin may show distinct changes on section [*69*]. The typical gross manifestations are best revealed by stretching the skin of the involved area taut. Fine yellowish nodules distributed along the natural skin lines are noted. Favorite areas, usually symmetrical, are the flexoral folds including the posterolateral part of the neck, axillary folds, antecubital fossae, inguinal areas and popliteal fossae. The disorder may also involve submammary, periumbilical and perianal skin, and the underside of the penis. It may give to these areas the appearance of a plucked chicken, Morrocan leather [*43*], or the outer skin of a lemon. Of interest is the occurrence in some patients of bouts of perinodular hyperemia [*16,17,32*] suggesting mild inflammatory episodes. During these times the area may be tender. Telangiectatic capillaries may serve to outline the lesions. This is especially true of mucous membranes, and indeed, involvement of the buccal, vaginal and rectal mucosa may occur.

Microscopically there is seen what Darier labelled "elastorrhexis." Fibers taking elastic stains are noted in the mid and deep corium to be swollen, fragmented and curled. Elastic staining material is greatly in excess of normal. Multiple fragments may give to the corium a granular appearance under low power. The occurrence of tuberculoid Langhan-type giant cells has been reported [*41,43*]. The finer reticulations of the subcutis or papillary area are not affected. The deposition of calcium in this degenerated material is thought to be common and has been demonstrated by microchemical means [*19,38*]. In one patient the calcium depositions gave an x-ray of subcutaneous calcinosis [*53*].

An excellent description of the fundus in this disorder has been recorded by Rizzuti [*48*]: "In the typical case the fundus presents a more or less complete peripapillary pigmented ring with off-shoots extending toward the equator in a radial distribution. In the early stages the streaks usually appear red but later may assume a gray, brown or black color. At times a white sheathing is seen in conjunction with the streaks which is probably of connective tissue origin. These streaks are flat, serrated, and may be several times wider than a retinal vein. They gradually taper off toward the periphery of the fundus where they may then appear as thin lines. They do not branch dichotomously as do the retinal vessels and in general they give the appearance of cracks in dry mud. The macular region is usually involved in varying degree with the presence of fresh hemorrhages, exudates, or old scars with excessive clusters of dark pigment. The periphery of the fundus may show an occasional chorioretinal lesion. There is frequently seen a dust-like pigment stippling which appears to be rather peculiar to the disease."

Scholz stressed the fact that 72 of the 188 patients with angioid streaks also have macular degeneration [*15*]. The finding of angioid streaks may therefore be a harbinger of serious eye as well as systemic illness. The onset of macular degeneration may be extremely insidious, as in the case of Coppez [*9*]; macular involvement developed eight years after the discovery of the streaks. The macular lesion may precede the development of angioid streaks [*73*]. It is also of interest that the characteristic stippling already noted may precede the development of angioid streaks. Bischler [*2*] considers the " 'mouchete' multicore" fundus as a "manifestation fruste" of the syndrome, when found in conjunction with pseudoxanthoma elasticum.

As pointed out by Rizzuti [*48*] and Scholz [*51*], a variety of abnormalities may simulate angioid streaks and this may account for the various theories as to their origin. These include: the "rosary" or "pearl chain" streaks due to pigmentation of sclerosed choroidal vessels; pigment streaks following retinal detachment; perivascular choroidal pigment atrophy; choroidal arteriosclerosis; and rupture of the choroid.

The few enucleated eye sections have yielded different findings [*36*].

Autopsied cases reported by Urbach and Bock [*3,67,68*] and Prick and Hagedorn [*25,44*] confirmed the presence of degenerative changes in the internal elastic membrane of the choroid (Bruch's membrane). The frequent breaks in this membrane were associated with a prominent basophilia. The connecting link of elastic tissue degeneration in both the skin and eye disorders now seemed established. Equally important, however, was the demonstration that similar degenerative changes of the connective tissue were manifest widely throughout the body, especially in the walls of blood vessels. As in Balzer's first autopsied case of pseudoxanthoma elasticum, plaques of degenerative tissue were noted in the endocardium and pericardium. The aorta, mesenteric arteries, coronary, cerebral and peripheral arteries in general were noted to show varying degrees of involvement, especially of the media but also of the internal elastic membrane. These studies served to focus attention on the systemic nature of the disorder.

In 1934 Ehlers [*17*] made a clinical study of a case of Grönblad-Strandberg syndrome and noted weak pulses and abnormal oscillometric findings. As cases accumulated, many were found to have hypertension, cardiomegaly, widening of the aorta, aneurysms [*3,54*], medial calcification as seen on x-ray film, and weak or absent peripheral pulses. These findings were correlated with angina, intermittent claudication, hemiplegias and subarachnoid hemorrhages, all occurring in an age group somewhat younger than expected [*24,54,69,77*]. Carlborg [*6*] in a classic study compared a younger group affected with this syndrome to both a normal group and an older group suffering from arteriosclerotic peripheral vascular insufficiency. He noted in ten of fifteen cases of pseudoxanthoma elasticum that the pulse wave velocity, the oscillometric index, and the pulse wave curve were similar to the findings in the group of patients with peripheral arteriosclerotic disease, despite the difference of fifteen to twenty years in their ages. Unlike peripheral vascular disease of arteriosclerotic origin, the upper as well as lower extremities may be involved in the Grönblad-Strandberg syndrome [*54*] Arteriosclerosis seems to occur in patients with this syndrome at an earlier age, resembling diabetes in that respect. Pathological evidence of involvement of the elastic tissue of large veins also has been presented. Carlborg [*6*] has made the interesting observation that in some of these patients, when performing the Valsalva maneuver, the jugular veins can distend to the size of an egg.

As noted previously the patient of Chauffard and Darier suffered several episodes of gastrointestinal hemorrhage. There are no other early reports of this association between pseudoxanthoma elasticum and gastrointestinal hemorrhage [*74*]. More recently a number of authors have emphasized this as a feature of the systemic disease [*30,39,46,47*]. McCaughey et al. [*42*] have recently pointed out that women with this syndrome are particularly prone to hemorrhage during pregnancy.

Pathological studies have revealed that the mesenteric vessels share in the degeneration of the elastin-staining tissue. In the case of Kaplan et al. [*30*] the vessels displayed beads of microaneurysms, thought to be the source of bleeding. The gastric mucosa itself revealed only superficial hemorrhages and erosions. Microscopic examination of the blood vessels revealed that the internal elastic membrane of the small and medium sized arteries of the gastric wall and adjacent gastrocolic and gastrohepatic ligaments exhibited selective degeneration.

Although gastrointestinal hemorrhage is the most serious form of bleeding, hemoptysis, epistaxis, bleeding gums, menometrorrhagia and hematuria have been recorded [*29*].

In 1933 Rowland first pointed out the association of angioid streaks of the retina with Paget's disease (osteitis deformans). In 1934 Terry [*60*] reviewed 108 cases of Paget's disease and found nine cases of angioid streaks. Later reviews of this association [*35,40*] showed that approximately 8 per cent of patients with Paget's disease have angioid streaks. In more recent times two well documented cases combining all three features of Paget's disease, angioid streaks and pseudoxanthoma elasticum have been reported by Woodcock [*78*] in 1952 and by Shaffer et al. [*53*] in 1957. There are other probable examples, such as that of Scheie [*54*] in which evidences of peripheral vascular disease were demonstrated.

Evaluation of the meaning of cases which combine this syndrome with other diseases is difficult and must await further clarification. For example, several cases of diabetes mellitus have been reported [*8,28,58*]. Hyperthyroidism also has been reported several times [*20,28*]. The

increased incidence of psychoses may be related to cerebral vascular involvement.

Although the evidence to date strongly supports the view that pseudoxanthoma elasticum is a systemic disorder, in many instances the degree of involvement of one system, for example the skin, may greatly exceed that of another system, for example the cardiovascular system. Hannay [*28*] reports a case in which the skin lesion was extremely marked with little or no evidence of cardiovascular involvement. On the other hand, minimal skin changes may be associated with severe repeated gastrointestinal hemorrhages. Revell [*47*] in reviewing the literature in 1948 listed in order of incidence the following findings in this syndrome: hypertension; inequality of and changes in the pulse; intermittent claudication or angina; evidence of calcification of the peripheral vessel as seen on x-ray film; abnormal bleeding into the gastrointestinal tract, uterus, bladder and brain; psychic disturbances and epilepsy. (Since he does not mention the eye complications in this listing, it would seem to that extent this testing is incomplete. It is probable that the order of frequency of symptomatic involvement in addition to the skin would be: cardiovascular manifestations; eye disturbances (amblyopia); hemorrhages, especially from the gastrointestinal tract; neurological manifestations; and endocrinopathies.)

Both the age and familial incidence of the disease are variable. It has commenced in childhood but generally develops between the second and fifth decades. DeSchweinitz [*12*] as early as 1896 collected significant examples of the occurrence of angioid streaks in sibships. Since then a considerable number have been accumulated. Touraine [*62–64*] has studied the hereditary pattern of the Grönblad-Strandberg syndrome. This seems to be variable irrespective of the clinical expression. It is thought that there is more than one genotype although in most instances it is autosomal recessive, partially linked to females. Occasionally, it is an autosomal dominant. Of course, the disorder may occur sporadically, without any evidence of familial incidence that can be detected.

As noted previously, the basic defect has been thought from the time of Darier to be a degenerative process of the elastic tissue. The discovery of the association with angioid streaks has lent favor to the view that the eye lesions likewise are defects in elastic tissue. In recent years several workers have challenged this view, notably Gilman [*21*], Hannay [*28*], Haber [*26*] and Sequeira [*52*]. McKusick [*43*] has carefully reviewed the arguments put forward for the view that the disorder is one of connective tissue which in the process of degeneration takes on certain staining characteristics of elastic tissue. It is pointed out that the most marked changes in the skin occur in the deep and mid-corium where in normal skin little elastic tissue is present. It is also contended that the blood vessels involved are mostly the muscular type with little elastic tissue. Although cases have been reported describing distinct changes thought to be of elastic tissue in the wall of the aorta, in the elastica surrounding the alveoli and in the internal elastic membrane of blood vessels, these have been discounted by skeptical observers because of lack of published photographs, etc. It is also argued that certain of the changes alluded to, for example the basophilia of Bruch's membrane, are non-specific, occurring in 10 per cent of enucleated eyes from a variety of disease entities. It is also noted that although the degenerative tissue stains similarly to elastic tissue, there are certain differences, as for example the manner in which it takes up Mallory's phosphotungstic stain [*21*]. Finally, the work of Tunbridge et al. [*66*] is cited in which the skin of patients with pseudoxanthoma elasticum was examined under the electron microscope and only slightly abnormal collagen fibrils could be found.

However, in support of the classical viewpoint are a number of facts. Other diseases characterized by degeneration of elastic tissue also are associated with excessive amounts of the tissue, as for example, colloid milium. Findlay's [*18*] work with elastase, despite certain arguments about the relative lack of specificity of the enzyme, is still difficult to refute when his work is examined carefully. He showed that the degenerative tissue in pseudoxanthoma elasticum is acted upon by this enzyme whereas collagen tissue is not. His technique included suitable controls. He also demonstrated that the degenerative material was not effected by hyaluronidase. He also noted that Weigert's stain protected the material in question against the action of elastase, just as it does with normal elastic tissue. This same relationship does not hold with hyaluronidase. The material in question also has a propensity for binding calcium, a recognized feature of degenerating elastic tissue.

Upon examining the work of Tunbridge et al. it is noted that collagen fibers are morphologically distinctive under the electron microscope whereas this does not seem to be true of elastic fibers which seem to be poorly outlined and much less distinctive. Also, as noted by the authors themselves, there was doubt about the success of teasing the degenerated tissue in question from the specimens of skin. It seemed highly likely that the fibrils resembling collagen in their studies were not the degenerative material they were attempting to study. Finally, the recent studies of Dr. Frank Law at Louisiana State University, as reported by Loria et al. [*39*], tend to support the notion that Tunbridge's technique was deficient. In describing electron microscope studies of a patient with the disease they reported the following: "The deposition of foreign matter in or on elastic tissue was evident on many sections studied. It was felt that marked selectivity and frequency of such involvement is much beyond the realm of chance." The collagen tissue in their studies appeared to be normal. The notable feature was that these workers were able to demonstrate elastic tissue with their technique and that this tissue appeared to be abnormal.

The controversy is further complicated by recent work being done by Tunbridge [*65*] and his co-workers at Leeds as well as work by Banga and Balo in Hungary. Their data suggest that, *in vitro*, collagen can assume the characteristics of elastic tissue, and vice versa. Incubation of collagen in borate buffer at pH 8 produced material indistinguishable from elastic tissue under the electron microscope. Normal elastic tissue when acted upon by elastin produces, at a certain stage, fibrils which under the electron microscope resemble collagen. It is known that with age certain tissues under constant stress, for example exposed skin surfaces, accumulate elastic tissue. Whether these recent *in vitro* findings have any bearing on *in vivo* changes of collagen into elastic tissue remains to be demonstrated. Gilman [*21*] has given evidence that radiation, trauma, etc., can cause "elastotic" degeneration of collagen fibers.

SUMMARY

The characteristics of pseudoxanthoma elasticum, and of its association with angioid streaks (Grönblad-Strandberg syndrome) are described. Evidence has accumulated that the disease is of systemic nature and may be associated with ambylopia, hemorrhage from gastrointestinal and other sites, coronary and peripheral vascular insufficiency, cerebral insufficiency and perhaps certain endocrinopathies.

Three relevant case reports are recorded, one resembling lupus erythematosus, another associated with Marfan's syndrome, and a third giving a history of repeated and severe gastrointestinal bleeding.

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D-Xylose and Its Use in the Diagnosis of Malabsorptive States*

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AMONG the numerous procedures employed in the diagnosis of malabsorptive states [*1*], only a few have been technically simple, widely applicable, inexpensive, and yet informative of the absorptive ability of the small intestine; these include plasma turbidity [*2–5*], carotene [*6,7*], and the urinary excretion of d-xylose after oral administration [*1–3,8–15*]. The present study was undertaken to evaluate the oral d-xylose test and to compare it with other indices of absorption in patients with malabsorption of varying etiology.

Physiologic Considerations. Substances employed to measure absorptive functions are subject to the same physiologic processes of intestinal absorption as foodstuffs, i.e., digestion, translocation and transportation. In addition, various metabolic processes referable to the specific test substance itself and the type of measurement often require special consideration. To facilitate an understanding of the biologic significance of the xylose test and its validity in evaluating intestinal absorption (especially carbohydrate absorption), a review of the metabolism of xylose seems appropriate.

Xylose is a five-carbon monosaccharide (pentose) with a molecular weight of 150. Foodstuffs such as fruits and grains are especially rich in pentoses and can produce an alimentary pentosuria [*16*]. As with most simple carbohydrates given alone or after digestion of a balanced meal, xylose is absorbed (translocated) primarily in the duodenum and proximal jejunum [*11*].

In healthy individuals an average of 65 per cent‡ of xylose is absorbed. After feeding the pentose, Fourman [*17*] could not recover any xylose by tube from the distal ileum. Benson and co-workers [*15*] state that in two well nourished patients with ileostomies (one year postoperative for ulcerative colitis) who were excreting normal amounts of xylose in the urine, "definite" quantities of xylose were recovered from the ileostomy drainage. Much of the unabsorbed xylose may be metabolized by the normal bacterial flora of the intestinal tract.

As it is a simple sugar, i.e., monosaccharide, no "digestion" is necessary prior to the absorption of xylose by the intestinal mucosa. Although specific studies as to the role of pancreatic secretions, bile and intestinal juices are not available, the results in various diseases provide inferential evidence that they are not of quantitative significance. As would be expected with a water-soluble substance, an emulsifier such as Tween 80® has no effect on xylose absorption [*14*]. Intraluminal conditions, such as near neutral pH, and possibly the presence of inorganic phosphate, may be important in the normal absorption of xylose. These two factors, together with intestinal motility, have been investigated principally in relation to glucose and other hexoses, and relatively infrequently with d-xylose. Ponz [*18*] demonstrated that the absorption of both xylose and glucose was decreased at either extreme of pH of the intestinal lumen (pH 3 or 10). The addition of phosphate buffer at pH 7 increased the rate of glucose absorption in rats [*19*]; although subsequent studies indicated that the action of phosphate was due to its pH [*20*], this work led to the phosphorylation theory (and subsequently including the hexokinase reaction) of carbohydrate absorption. The effect of intestinal motility upon xylose absorption ap-

‡ This figure actually represents the quantity of xylose reaching the blood. It is exclusive of any amount metabolized during the process of translocation above that which is metabolized by the intestinal mucosa upon delivery from the systemic circulation. This amount presumably is so small from the clinical point of view that it is disregarded for these purposes.

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parently has not been evaluated, although studies in man with other saccharides are available [*21*]. An investigation of glucose absorption in drug-induced hypermotility indicated an increased rate of glucose absorption during hypermotility [*22*]. However, it seems likely that the hypermotility associated with diseased small intestine, e.g., terminal ileitis, decreases xylose absorption, at least in some cases.

Whether d(+)xylose is actively absorbed and whether this involves phosphorylation and/or specific enzymes is not clear. The uncertainties arise because studies to "prove" active or passive (by diffusion) absorption have: (1) often not specified which xylose was being used or l-xylose was employed. Larson et al. [*23*] demonstrated that d-xylose is absorbed at many times the rate of l-xylose; (2) been based upon the comparative hexose-pentose absorption, employing phlorizin and monoiodoacetic acid (which are controversial as specific poisoners) inhibition of the hexokinase reaction. Sols' [*24*] recent experiments have documented the contention of those who found the hexokinase-phosphorylation theory inadequate to explain carbohydrate absorption. His findings limit the hexokinase reaction to the initiation of glycolysis of the carbohydrate for the need only of the mucosa itself and not as a part of the absorptive process; (3) attempted to ascribe *in vitro* results to *in vivo* mechanisms. Davidson and Garry [*25*] reported that both d- and l-xylose behave dissimilarly *in vivo* and *in vitro;* (4) been derived from conclusions based on indirect evidence. Fourman [*26*] considered the proportional fall of serum inorganic phosphate during fructose and glucose absorption to be indicative of active absorption. Turner [*14*] and Brien et al. [*13*] demonstrated the same effect with glucose and xylose. Wyngaarden, Segal and Foley [*27*] reported that this fall also is proportional to the rate of carbohydrate infusion intravenously, i.e., changes in blood xylose level, thus providing another and probably a predominant mechanism for the serum phosphate changes.

Xylose is not transported against a concentration gradient and its disappearance rate from the intestine is directly proportional to its intraluminal concentration [*28*]. Verzar and McDougall [*29*] list the relative rates of absorption of sugars as galactose > glucose > fructose > pentoses. Traditionally, it is considered that the hexoses are absorbed actively and the pentoses absorbed passively, i.e., by diffusion. Many authors maintain this view as well as the phosphorylation theory. Others [*26,30,31,32*] believe that at least d-xylose (of the pentoses) is absorbed actively and they present data indicating its phosphorylation during absorption. Turner [*14*], in commenting upon Hele's ability to phosphorylate xylose *in vitro* with rat mucosal extract in the presence of added inorganic phosphate and ATP [*30*], suggested the probability of a specific xylokinase in mucosal tissue.

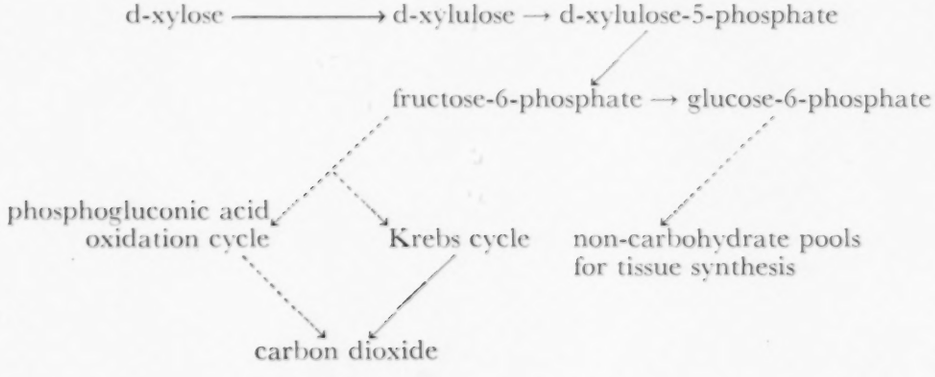
In common with most other water-soluble substances, xylose probably is transported from the serosal aspect of the intestinal mucosal cell to the systemic circulation via the portal vein and the liver. Animal studies illustrating the influence of endocrines on xylose absorption have been reported by Althausen and Stockholm [*33*], who produced a marked increase in xylose, galactose and glucose absorption after the basal metabolic rates in rats given thyroid had been increased by 50 per cent. Others [*34*] showed that adrenalectomy in rats did not influence the absorption of xylose, although glucose absorption was depressed. The same relative effects upon xylose and glucose absorption were found in vitamin B-deficient rats [*35*].

Following the ingestion of d-xylose, the blood xylose level reaches a peak at one or two hours, and, in linear fashion, approaches fasting values at the end of five hours [*13–15*]. After the oral administration of 25 gm. of d-xylose to normal persons, the average maximum blood concentration is approximately 35 mg./100 ml. [*13,15*]. Approximately 6.5 gm. are recoverable in a five-hour collection of urine, therefore the remaining 18.5 gm. must be attributed to non-absorption, delayed absorption (hence excretion is delayed) and/or utilization by the body. In the absence of disease, delayed absorption-excretion is unlikely. Previous workers [*13,14*] have established that in normal persons significant amounts of xylose are not excreted after five hours. As stated earlier, approximately 65 per cent (or 16.25 gm.) of the xylose is absorbed, leaving an appreciable quantity attributable to utilization by the body.

Xylose (also other pentoses and various hexoses) can be recovered routinely from the urine in man [*36*]. The several investigations employing intravenous infusion of d-xylose are in agreement concerning the renal excretion of xylose in man. Approximately 40 per cent of the pentose is recoverable in the urine. Radioactive carbon studies with xylose-1-C^{14} give com-

parable but slightly higher values, and also indicate that this substance is utilized similarly to unlabeled xylose [*27*]. The constancy of renal excretion of xylose has led to its suggested use as a renal function test; its advantages over the frequently employed phenolsulfonphthalein and other procedures are discussed by Fishberg and Friedfeld [*8*]. The rate of disappearance of xylose from the blood is proportional to the plasma concentration. Furthermore, the total amount excreted is a constant fraction of the amount infused [*8,27*] This constant fraction (40 per cent) is a function of the glomerular filtration rate, although some xylose is reabsorbed by the renal tubules [*27*]. Studies with radioactive xylose demonstrated that virtually all the isotopic substance was present as the unaltered pentose and excluded the occurrence of appreciable quantities of xylose metabolites [*27*]. The mechanism of renal excretion is the same after xylose is given either orally or intravenously [*37*].

Although previous investigators [*8,10*] have considered that d-xylose is not metabolized, recent work leaves little doubt that d-xylose is metabolized in man. Approximately 60 per cent of the infused xylose could not be recovered in the urine [*27*]. The manner or route of the metabolic process is obscure. An evaluation of the many studies contributing indirect or inferential data on the utilization of xylose by the body is beyond the scope of this paper. However, the hypothesis of Wyngaarden and coworkers [*27*] represents an acceptable recent "working" concept. In essence:



Approximately 20 per cent of the infused xylose could be recovered as carbon dioxide. The remainder (40 per cent) not excreted was considered to have entered non-carbohydrate pools. The degradation to carbon dioxide is quite rapid (within fifteen minutes) but the conversion to glucose apparently is considerably slower. Phosphorylation probably plays a role in xylose metabolism, as do high energy systems, e.g., ATP. Several authors [*27,31,38*] have suggested that the similarity of glucose and d-xylose at the 1,2 carbon positions is partly responsible for the manner of metabolism. In view of the possible correlation of glucose and xylose metabolism, it is interesting that the rate of xylose metabolism in diabetic persons deprived of insulin is unchanged [*39*] and the urinary excretion of xylose is normal [*40*]. Our findings are in agreement. It has been established that the ratio of metabolism to excretion is constant (60:40) and the rate is a function of the plasma levels [*11,27*].

The role of the liver in xylose metabolism is not clear. Negative evidence was obtained in animals with known liver disease [*8*], but the disappearance of xylose in the blood is considerably slower in cirrhotic subjects [*27*]. In patients with hepatic disease, Benson et al. [*15*] found slightly decreased urine values. Our studies reveal no consistently abnormal results after the oral administration of xylose in patients with uncomplicated hepatic disease.

Segal et al. [*38*] considered that the abrupt lowering of the blood xylose after the administration of insulin was a function of increased intracellular distribution and not of increased hepatic metabolism. D-xylose is distributed throughout the extracellular fluid and is present to some extent in intracellular compartments.

METHOD

The test usually was initiated between 6 and 8 A.M.; nothing was ingested orally after the previous midnight (or previous eight hours) until the completion of

TABLE I
FIVE-HOUR URINARY XYLOSE EXCRETION AFTER ADMINISTRATION OF 25 GM. ORALLY

Authors	Patients (no.)	Mean ± S.D. (gm.)	Range (gm.)
Normal Subjects			
Brien et al. [13]	12	6.14 ± 0.70	5.0–7.2
Gardner and Perez-Santiago [3]	42	5.6 ± 0.6	.....
Benson et al. [15]	25	6.5 ± 1.2	4.1–8.2
This report	10	6.76 ± 0.88	5.6–8.2
Patients with Tropical Sprue (Untreated)			
Gardner and Perez-Santiago [3]	13	1.5 ± 0.9	.....
Patients with Malabsorption Syndrome (Untreated)*			
Gardner [2]	19	2.2 ± 1.3	.....
Patients with Idiopathic Malabsorption or Non-Tropical Sprue (Untreated)			
Benson et al. [15]	5	1.3 ± 0.7	0.8–2.6
This report	9	1.8 ± 0.6	0.6–2.4

* Military personnel, mostly native American, on duty in Puerto Rico. No anemia.

the procedure, except as will be indicated. The residual urine was discarded. Twenty-five grams of d (+) xylose (Fisher), dissolved in 500 cc. of tap water, was given. An additional 250 cc. of water was administered at one and at two hours. Five hours after the xylose was ingested, the patient voided and this specimen was added to any urine passed during the five-hour period. The combined specimen was refrigerated or analysed immediately.

The xylose content of the urine was determined by the method of Roe and Rice [11]. All subjects had normal renal function, as estimated by normal urinalysis, ability to concentrate urine and/or a normal blood urea nitrogen. Practically all patients excreted more than 150 cc. of urine during the five hours, as suggested by Gardner and Santiago [3]. Basal metabolic rates were within the normal range in all the patients examined.

Plasma carotene was determined by the Yudkin modification of Kimble's method, as described by Wenger et al. [6]. Fecal fat excretion was based on a relatively constant fat intake of 70 gm. per day (as estimated from standard tables) for five days and stool collections during the last seventy-two hours. On analysis, the fat content of the meals was found to be within 10 per cent of the estimated amount. The output of fat in the feces was measured by the Van de Kamer method [12]. To maintain a constant index, fat absorption is expressed as a coefficient of absorption (C.A.), utilizing the fecal fat results* and calculated according to the equation:

$$\text{C.A.} = \frac{\text{Average 24 hour fat intake (gm.) less average 24 hour fecal fat (gm.)}^*}{\text{Average 24 hour fat intake (gm.)}} \times 100$$

The xylose, carotene and fecal fat determinations (and other absorptive tests) were performed during the same stage of the disease (usually within a five-day period) to facilitate more accurate comparison.

Almost all patients were investigated initially during active stages of their disease usually characterized, in part, by diarrhea. Individuals with idiopathic malabsorption were studied before and in some instances after therapy comprising steroids and/or gluten-free diet. Some of the patients with regional enteritis or ileocolitis were receiving steroids at the time of evaluation.

DISCUSSION OF METHOD

The xylose test was performed under fasting conditions to avoid competition with other foodstuffs for absorptive mechanisms. When the xylose was given up to two hours before or after a "normal" breakfast, in preliminary experiments, the decrease in urinary xylose excretion under non-fasting conditions averaged 10 per cent. Benson and co-workers [15] reported a decrease in blood levels and "flattening" of the xylose blood curve when other absorbable foodstuffs were fed simultaneously with xylose. Twenty-five grams of xylose was prescribed to obtain reproducible results and to lessen the tendency to diarrhea observed after the administration of larger amounts [10,13]. When 10 gm. of xylose was given in preliminary studies, excretion in four normal subjects varied from 22 to 39 per cent of intake; repeated testing in a single individual produced values from 22 to 30 per cent. Our observations of the reproducibility of the values for xylose in urine in the same individual and the optimum period of collection after the administration of 25 gm. of xylose orally substantiate the findings of others [13,14].

The 25 gm. of xylose was dissolved in 500 cc. of water to achieve approximate isotonicity and thus avoid sudden shifts in extracellular fluids. Although additional quantities of water were given at one and two hours, the intake of varying amounts of water (0 to 1,000 cc.) made no difference in the total five-hour xylose excretion in three normal persons.

Only five-hour urine collections were made routinely in this study. While previous workers found xylose curves useful, urine values were more reproducible, with less overlapping of normal and abnormal results [2,13,15]. In agreement with others [15], determinations on refrigerated urine after one week or longer gave the same values as immediate analysis. The xylose content was unchanged in urine allowed to stand at room temperatures for twenty-four hours, essentially confirming Fourman's report [12]. We found it helpful to print the directions for the procedure on the envelope into which the measured

TABLE II

FIVE-HOUR URINARY XYLOSE EXCRETION IN VARIOUS GASTROINTESTINAL DISORDERS

Disorder	Patients (no.)	Average or Mean ± S.D. (gm.)	Values or Range (gm.)
Normal	10	6.76 ± 0.88	5.6–8.2
Functional bowel distress	17	6.3 ± 1.6	(2.8) 4.3–8.8
Functional bowel distress with duodenal deformity	5	5.0	4.1–7.2
Idiopathic malabsorption (untreated)	9	1.8 ± 0.6	0.6–2.4
Multiple jejunal diverticula	2	2.6	1.7, 3.4
Regional enteritis or ileocolitis with steatorrhea	6	4.6	(2.2) 4.0–4.5 (8.3)
Regional enteritis or ileocolitis without steatorrhea	6	5.8	4.0–6.2 (9.3)
Ulcerative colitis	5	7.6	6.0–7.5 (10.7)
Recurrent regional enteritis after small bowel resection with ileocolostomy	4	5.1	4.1–6.6
Liver disease with jaundice	4	9.0	8.5–9.4
Pancreatic disease	3	5.7	5.0, 5.9, 6.1

25 gm. of xylose was placed for instruction of the nursing staff and the patient.

The relatively simple method of Roe and Rice is specific for pentoses and was quite reproducible in multiple determinations on a single specimen or in recovery studies. Although not as sensitive as the orcinol-ferric chloride pentose determination [*27*], the present (p-bromaniline) method is more specific, as the former measures pentose metabolites, glucuronic acid and certain other substances. Wyngaarden et al. [*27*] found excellent agreement in urine values when employing both methods.

RESULTS

Table I lists the values for the ten normal subjects studied, together with previous reports employing the same method throughout. There is rather close agreement in the four groups. The vast majority of normal persons excrete in excess of 5.0 gm. of xylose within five hours.

Idiopathic Malabsorption (Non-tropical Sprue). All except one of the nine untreated patients (Tables I and II) and of the total eleven patients in this category in Table III are considered to have "gluten-induced enteropathy," as described by Frazer [*43*] and have responded to therapy with a gluten-free diet and/or steroids. The values of less than 2.5 gm. in the nine untreated patients with idiopathic malabsorption are almost identical with the reported results in (non-tropical) "sprue" and tropical sprue. (Table I.) Only four other patients of the one hundred tested with xylose had values lower than 2.5 gm.*

The urinary xylose excretion increased after treatment (steroids or gluten-free diet, and supportive therapy) in three patients in whom comparative studies were obtained. (Table III.) However, the values were definitely low in four of five patients tested during treatment. (Table III.) Four of the five treated patients with idiopathic malabsorption had gained weight, and generally were asymptomatic at the time of the repeated xylose determination.

Other Malabsorptive States and Miscellaneous Diseases. The interesting malabsorption associated with multiple small intestinal diverticula is one of a few conditions producing xylose values, below 2.5 gm. or 10 per cent (of the oral xylose dosage). The two patients in the present series excreted 1.7 and 3.6 gm. of xylose during a period of diarrhea and weight loss. (Table IV.)

In patients with active regional enteritis and ileocolitis, the results varied considerably. However, the average value among those with an associated steatorrhea was abnormal (4.6 gm.), while in those without steatorrhea results were in the normal range. (Table II.) In five patients with active ulcerative colitis, an average of 7.6 gm. of xylose was recovered in the urine; only one had steatorrhea. Four patients with previous small bowel resection and ileocolostomy were studied at a time of reactivation of the regional enteritis; the values in this group ranged from 4.1 to 6.6 gm.

Since most patients in whom gastric surgery

* The four exceptions were: J. W. (Table IV); a patient with ileocolitis and associated steatorrhea; a cirrhotic patient with ascites; and a patient with pronounced iron-deficiency anemia, subtotal gastric resection and partial small bowel resection.

TABLE III

COMPARATIVE RESULTS OF TESTS IN PATIENTS WITH IDIOPATHIC MALABSORPTION

Patient	5-Hour Urinary Xylose (gm.)	Plasma Carotene (μg. per 100 ml.)	Coefficient Fat Absorption (%)	Small Bowel X-rays	Schilling Test (% $Co^{60}B_{12}$ 24 hr. urine)	Glucose Tolerance Test (maximum rise mg. %)	Macrocytic Anemia (less than 12 gm. hemoglobin)	Small Intestinal Biopsy
Normal	6.76 ± 0.88	70–320	Greater than 93	–	7–25%	Greater than 40	–	...
L. L.	2.0	44	53	+	.....	15	–	...
B. L.	1.2	23	52	+	.....	18	–	...
M. Mz.	2.0	54	88	+	.....	.....	–	+*
B. W.	2.0	16	89	+	.....	7	+	...
N. S.	2.4	17	56	+	.....	60 (delayed)	–	...
W. C. (Asymptomatic no Rx)	2.3	99	89	–	.....	.....	–	+*
D. J.	0.6	3	60	+	0.4	.....	+	...
After Rx	2.6	92	.....	+	.....	.....	–	...
M. Mc.	1.8	29	80	+	.....	.....	–	...
After Rx with partial response	3.4	79	98	+	2.4	69 (delayed)	–	+
E. K.	2.3	4	87	+	7.3	17	+	...
After Rx with good response	7.0	215	94	+	.....	80	+	...
M. Q. (asymptomatic on Rx)	2.4	43	91	+	.....	.....	–	...
L. H. (asymptomatic on Rx)	4.1	171	.....	–	.....	.....	–	...

* Shiner tube biopsy.

had been performed had other disorders, such as hepatic disease or other bowel surgery, the effect of gastric surgery (i.e., gastric resection, gastroenterostomy) alone upon xylose absorption could not be determined. One patient with a total gastrectomy eliminated 6.4 gm. of xylose in the urine.

Results of the xylose test in three patients with pancreatic disease, proved histologically, were normal or near normal (5.0, 5.9 and 6.1 gm.); the last figure was obtained in a patient with a total pancreatectomy. (W. C., Table IV.)

Table II lists four patients with jaundice and elevated urine xylose levels (8.5 to 9.4 gm.). Three of the four had hepatitis and the fourth had mild portal cirrhosis. Several other patients with portal cirrhosis and a variety of other chronic hepatic diseases were studied; the results were highly variable. Most patients with chronic liver disease had additional conditions, such as previous bowel surgery complicating the evaluation. However, the impression gained from this unlisted group is that chronic liver disease has little primary effect on the results of the five-hour urine xylose procedure. Ascites usually was associated with a low urine xylose. One patient with cirrhosis and ascites excreted only 1.6 gm. of xylose in five hours; the concentrations of xylose in the blood and in the ascitic fluid were similar.

Twenty-four patients with functional bowel distress were investigated. In seventeen with

completely negative gastrointestinal studies, including gastrointestinal x-rays, the mean urinary xylose was 6.3 gm. Five persons who had a previous history of duodenal ulcer, without activity on current x-rays, excreted an average of 5.0 gm. of xylose. (Table II.) Two patients with irritable digestive tracts, who also had a duodenal diverticulum, excreted 3.8 and 4.0 gm. of xylose, respectively.

In three diabetic subjects in whom the administration of insulin was omitted prior to the test, xylose values were in the normal range.

The effect of steroids upon xylose absorption-metabolism-excretion cannot be determined from the present study. The similar results in two patients with ileocolitis before and after the administration of steroids, and the lack of change in the urine xylose in one normal person after five days of prednisone, 20 mg. administered per day, suggest that steroid therapy had little effect. This may not be true in idiopathic malabsorption treated with steroids; the period of observations, furthermore, is too brief.

Comparison with Other Absorption Tests. Fat Absorption and Carotene. (*Table* V.) The standard reference test of malabsorption has been the determination of fecal fat. This procedure was performed in most cases of this series. Both the xylose and the fat measurement presented evidence of malabsorption in all the untreated patients with idiopathic malabsorption. (Table III.) However, there was no correlation between the degree of fat and of xylose malabsorption. The xylose values generally remained definitely abnormal in treated patients with idiopathic malabsorption, although coefficients of fat absorption were normal or nearly normal.

The plasma carotene was measured in practically all patients. Except in an asymptomatic patient not receiving treatment (W. C., Table III), the carotene values in the untreated patients with idiopathic malabsorption were significantly below normal; in six of the nine untreated patients, within the "severe depletion" range, i.e., below 30 μg. per cent [6]. Xylose values could not be correlated directly with the "depletion" level of plasma carotene in the

TABLE IV

XYLOSE, CAROTENE AND FAT ABSORPTION VALUES IN PATIENTS WITH VARIOUS GASTROINTESTINAL DISORDERS

Patient	Disease	5-Hour Urinary Xylose (gm.)	Plasma Carotene (μg. per 100 cc.)	Coefficient Fat Absorption (%)
C. R.	Multiple jejunal diverticula	3.4	50	50
J. W.	Multiple jejunal diverticula	1.7	79	92
J. F.	Ileocolitis	4.5	23	82
P. P.	Regional enteritis	4.4	92	77
A. A.	Ileocolitis	8.3	40	20
	After three days of steroid and Pamine therapy	6.7	...	70
M. M.	Ileocolitis	6.2	54	95
P. L.	Regional enteritis	4.6	53	97
F. M.	Ulcerative colitis	7.5	96	99
W. C.	Total pancreatectomy	6.1	...	69
J. G.	Pneumatosis cystoides intestinalis	7.3	167	..
R. F.	Gastroenterostomy with multiple absorption defects	3.4	20	87
M. B.	Recurrent regional enteritis after ileal resection with ileotransverse colostomy	5.7	41	75
H. C.	Recurrent regional enteritis after ileal resection with ileotransverse colostomy	6.6	134	72
M. N.	Recurrent regional enteritis after ileal resection with ileotransverse colostomy	4.1	44	..
B. R.	Recurrent ileocolitis after ileoproctostomy	4.3	66	88

TABLE V

COMPARISON OF RESULTS OF ABSORPTION TESTS

Disease	Patients (no.)	5-Hour Urinary Xylose (gm.)	Plasma Carotene (μg. per 100 ml.)	Coefficient Fat Absorption (%)
Normal	..	6.76 ± 0.88	70–320	>93
Idiopathic malabsorption	9	1.8	31	75
Diverticula of jejunum	2	2.6	65	71
Regional enteritis or ileocolitis with steatorrhea	6	4.6	70	70
Regional enteritis or ileocolitis without steatorrhea	6	5.8	90	>93
Recurrent regional enteritis after ileal resection and ileocolostomy	4	5.1	71	78
Ulcerative colitis	5	7.6	78	>93

untreated patients. Table III illustrates the restoration of the plasma carotene and of fat absorption to normal during treatment; this response was not as evident with the xylose test.

Table V lists the average values for xylose, carotene and fat absorption in groups of patients with diseases of the small and/or large intestine, and Table IV the results of the three tests in specific patients with a variety of gastrointestinal disorders. The relative impairment of xylose absorption is poorly correlated with the degree of steatorrhea and the carotene values in the two patients with jejunal diverticula. (Table IV.) One patient (J. W.) had a markedly low xylose 1.7 gm., normal carotene and borderline steatorrhea; whereas another patient (C. R.) with a "moderately depleted" plasma carotene, 50 μg., absorbed only 50 per cent of the fat intake, and the urine xylose was moderately reduced (3.5 gm.).

As stated earlier, in patients with regional enteritis or ileocolitis, the average xylose outputs were reduced in those with associated steatorrhea. (Table V.) The low xylose values did not correlate consistently with the abnormal fat absorption. There was considerable overlap in xylose and carotene data between the two groups of patients with the same diseases; and in individual patients within each group. For example, in one patient (A. A., Table IV) the xylose value was high and fat absorption was extremely poor. On treatment, the xylose output was normal and fat absorption improved markedly.

The four patients with recurrent regional enteritis or ileocolitis following partial resection of the ileum (up to 5 feet) and ileocolostomy were receiving steroids. In the three in whom fat balance studies were made, the average percentage of fat absorption was 78. The xylose and carotene figures for the four averaged 5.1 gm. and 71 μg., respectively. No specific correlation existed between the results of the xylose, carotene or coefficient of fat measurements. (Table V.)

In all but one of the five patients with active ulcerative colitis (Table V) the coefficient of fat absorption, urine xylose and plasma carotene were normal. Similar studies in several other patients with ulcerative colitis (not included because of possibly complicating coexistent conditions) suggest that xylose and fat absorption usually are normal, although carotene values tend to be moderately decreased.

Three patients with pancreatic disease were evaluated. (Table II.) Urinary xylose excretion exceeded 5.0 gm. in all three. Only one patient (W. C., Table IV), who had undergone a total pancreatectomy for pancreatic carcinoma, had steatorrhea. Prior to operation he absorbed only 50 per cent of dietary fat and the plasma carotene was 40 μg. During therapy with pancreatic extract postoperatively, the coefficient of fat absorption was 69 per cent and the urinary xylose (administration of pancreatic supplement and insulin omitted during the test) was 6.1 gm. Fecal fat and plasma carotene were normal in the other two patients with pancreatic disease, although one of these had previously had steatorrhea.

Other Absorption Tests and Procedures. In addition to the three standard procedures other methods were performed in selected cases. In two patients with idiopathic malabsorption (D. J. and E. K., Table III) and macrocytic anemia the recovery of orally administered radioactive vitamin B_{12} in the urine was abnormal; however, the results of Schilling tests did not correlate consistently with the xylose data. The oral glucose tolerance test was performed in five untreated patients with idiopathic malabsorption. Four of the five manifested very little increase (less than 18 mg. per cent) in the blood sugar levels and the fifth had delayed but adequate blood sugar rise (40 mg. per cent) after the oral administration of glucose. Following therapy with steroids and gluten-free diet in one patient with idiopathic malabsorption (E. K.) results of both the glucose tolerance test and the xylose test were normal. Jejunal biopsy specimens, obtained via the Shiner biopsy tube, in two patients were compatible with the histologic findings of non-tropical sprue.

The glucose tolerance test also was performed in fifteen non-diabetic patients. Table VI lists the results of the xylose, oral glucose tolerance and fat absorption tests in five individuals of this group. In two patients (M. W. and H. C.) results of the glucose tolerance test were abnormally low while the xylose and fat balance results were normal. A third patient (P. P.) demonstrated only mild depression of xylose excretion, whereas the other two absorption tests suggested considerably decreased absorption.

Two patients with abnormal xylose values deserve special mention. One patient (M. Mc., Table III) is included in the group with idiopathic malabsorption. She is the only patient

TABLE VI

COMPARISON OF RESULTS OF CARBOHYDRATE ABSORPTION TESTS

Patient	Disease	5-Hour Urinary Xylose (gm.)	Glucose Tolerance Maximum Rise (mg. %)	Coefficient Fat Absorption (%)
J. K.	Functional bowel distress with duodenal deformity	4.3	52	..
M. W.	Regional enteritis	6.1	18	97
P. P.	Regional enteritis	4.4	14	77
M. N.	Recurrent regional enteritis after ileal resection and ileo-transverse colostomy	4.1	51	..
H. C.	Xanthoma-siderohistiocytosis	5.9	39 (delayed)	95

with this diagnosis who did not respond to treatment with a gluten-free diet and/or steroids. Multiple absorption tests indicated significant impairment of absorption, and barium x-ray studies revealed a marked disorder in the motility of the stomach and upper small intestine. At operation, jejunal and ileal biopsy specimens demonstrated only slight abnormality of the mucosa but pronounced degeneration of the longitudinal muscle layer. In the second patient (R. F., Table IV) results of the xylose test were abnormal (3.4 gm.), fat absorption was impaired (87 per cent) and the plasma carotene was severely depleted (20 μg.). In this patient (R. F.) only 2 per cent of $Co^{60}B_{12}$ was recovered in a twenty-four-hour urine collection (despite the administration of intrinsic factor and antibiotics). In addition a defect in the absorption of iron was considered to be present. Biopsy specimens from various levels of the jejunum failed to reveal histologic abnormalities.

COMMENTS

The oral glucose tolerance test has been the traditional index of carbohydrate absorption from the intestine. In addition to its obvious disadvantages, recent reports [*3,43*], indicating the high proportion of "flat curves" in healthy subjects, have emphasized further the need for a simpler and more reliable test of intestinal absorption of carbohydrates. In many respects the xylose test fulfills this need. Previous studies [*3,13,15*] indicate that the average two-hour blood level of xylose after the ingestion of 25 gm. of xylose was approximately 35 mg. per cent. However, the ranges of normal were considerable and tended to overlap in the range of idiopathic malabsorption. The five-hour urinary values provide much sharper definitions of normal and abnormal. If renal disease is suspected, the finding of a two-hour blood value above 25 mg. per cent is helpful in estimating normal xylose absorption.

The standard dose of xylose has been 25 gm. In agreement with others [*15*] we found that the clinical symptoms after the ingestion of xylose varied from minimal borborygmi in most instances to mild abdominal cramps with a temporary increase in diarrhea in a few patients. A dosage of 0.5 gm. per pound of body weight up to 25 gm. has been recommended in children [*44*]. As little as 2.5 gm. of xylose apparently can be used adequately [*45*].

The stability of xylose in the urine permits an ambulatory procedure, when necessary. The cost of the test dose of xylose is nominal and the equipment, materials and time required to perform the determination permit extremely wide application of the procedure.

The xylose test is most efficacious as a screening test for idiopathic malabsorption. Patients with "sprue syndromes" have clearly defined low values, usually below 2.5 gm. (or 10 per cent). Urine xylose values remain low despite treatment, as found by others [*3,15*] and in our series. An example of the use of the xylose test as a screening procedure for idiopathic malabsorption is illustrated by a patient (W. C., Table III) who was essentially asymptomatic, but whose past history of severe diarrhea and weight loss without pain suggested malabsorption. Despite a normal plasma carotene and normal findings on gastrointestinal roentgenograms, a urine xylose of 2.3 gm. prompted further studies; these revealed a slight decrease in fat absorption (89 per cent) and histologic evidence of non-tropical sprue as observed on a small intestinal biopsy specimen. Infrequently, other

untreated patients with gastrointestinal diseases will excrete less than 2.5 gm. of xylose but most of these problems can be easily differentiated from idiopathic malabsorption, usually on the basis of the radiologic examination. Among the conditions associated with low xylose values not differentiated or diagnosed by x-ray films are Whipple's disease, and non-Addisonian macrocytic anemia [*15*]. The low urine values in idiopathic malabsorption may reflect in part delayed as well as decreased xylose absorption. Fourman [*17*] found in one patient with nontropical sprue a five-hour urine xylose recovery of 1.38 gm. while a twenty-four-hour urine collection yielded 3.08 gm.; usually appreciable amounts of xylose cannot be recovered normally after five hours.

Another clinical application of the xylose test is in establishing the etiology of steatorrhea. Patients with pancreatic insufficiency and poor fat absorption do not have impaired xylose absorption. Benson and co-workers [*15*] described five patients who required treatment for pancreatic exocrine insufficiency, with urinary xylose values of 6.0, 6.5, 6.9, 10.0 and 10.0 gm. Thus "pancreatic steatorrhea" can be distinguished from idiopathic malabsorption. The xylose results in patients with fat malabsorption complicating regional enteritis and ileocolitis generally are lower (average 4.6 gm.) than in those with pancreatic disease, and usually are separated readily from those with idiopathic steatorrhea.

Definite impairment of xylose absorption (below 4.0 gm.) seldom is encountered without other positive indications of malabsorption. However, a slightly low xylose value (4.0 to 5.0 gm.) cannot be used to estimate the presence of steatorrhea even when the disease has been diagnosed. For example, although the average xylose results in patients with regional enteritis or ileocolitis and associated steatorrhea are lower than in a similar group without steatorrhea, the overlap in our few cases is considerable. (Table II.) Perhaps the variable xylose values in regional enteritis reflect varying degrees of intestinal hypermotility.

SUMMARY AND CONCLUSIONS

The normal metabolic fate of d-xylose in the body is described as a background for evaluating the use of xylose as a test of intestinal absorption.

The test is performed by measuring the excretion of d-xylose in the urine after the oral administration of 25 gm. The results of the xylose test in more than 100 patients have been compared with other measurements of intestinal absorption in the same patients, and indicate the wide applicability and the relative simplicity of the procedure.

Less than 2.5 gm. of xylose (10 per cent) are excreted in a five-hour urine collection in patients with untreated idiopathic malabsorption; xylose excretion usually remains low despite treatment. Other tests in untreated patients with idiopathic malabsorption also demonstrate defective absorption of carotene, fat and glucose. In patients with pancreatic disease the xylose test is normal although other absorptive tests, e.g., fat absorption, may be abnormal. The results of fat absorption, carotene and xylose tests do not correlate consistently in any condition other than idiopathic malabsorption. Except in patients with idiopathic malabsorption, few subjects excrete less than 2.5 gm. of xylose.

The d-xylose test appears to be the most useful screening procedure for identifying idiopathic and secondary types of malabsorption or steatorrhea currently available.

Acknowledgment: We wish to thank Dr. Walter L. Palmer and members of his staff for their cooperation in this study.

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Review

Rheumatism and Psoriasis*

A Re-evaluation

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FOR many years there has been much discussion about the association of rheumatism and psoriasis. Some authors have maintained that there is a definite entity, "psoriatic arthropathy" [*18,23,37,38*], while others have considered these cases merely to represent the chance coincidence of two common diseases, psoriasis and rheumatoid arthritis [*7,21*]. As recently as 1957 Short, Bauer and Reynolds [*39*] expressed the view that the conception of psoriatic arthritis as an independent disease seems unwarranted. The difficulty in assessing the incidence of the association of rheumatism and psoriasis is indicated by the diverse figures in the literature [*3,8–11,21,25,28,30,32–34,41*]. Although there seems to be general agreement among dermatologists that the incidence of atrophic arthritis is higher in patients with psoriasis than in the general population their figures often only border on statistical significance.

In recent years workers with the Rose-Waaler sheep cell agglutination test (S.C.A.T.), in which results are positive in some 80 per cent of patients with rheumatoid arthritis [*20,29*], have commented that in patients who had psoriasis with atrophic arthritis the results were usually negative [*1,12,26,46*]. From a study of data on thirty-nine patients it was suggested that patients with psoriasis and erosive arthritis who have a negative S.C.A.T. either have rheumatoid arthritis modified in the presence of psoriasis or, what is more likely, constitute a distinct entity [*44,45*]. This series, however, was large enough only to make tentative suggestions, it did not allow statistical analysis, and did not include control groups.

MATERIAL AND METHODS

Data on 154 patients with psoriasis and various rheumatic complaints have been studied. In all patients the diagnosis of psoriasis was confirmed by a dermatologist. Ninety-five of the patients with psoriasis and erosive arthritis were paired with patients of the same sex and age who had uncomplicated rheumatoid arthritis of the same duration, and a positive S.C.A.T. Eighty-five of the patients with psoriasis and erosive arthritis were paired with patients of the same sex and age who had psoriasis of the same duration. The modification of the S.C.A.T. introduced by Greenbury et al. [*20*] was employed in testing the serum of all patients.

GENERAL REVIEW OF RESULTS

Of the patients with psoriasis and rheumatic complaints there were twenty-three (nine men, fourteen women) with osteoarthritis, two men with gout, two men with rheumatic fever and nine (five men, four women) with muscular rheumatism. In these patients without erosive arthritis there were no unusual features of the skin or joint condition and their association seemed fortuitous. There were 118 patients with psoriasis and erosive arthritis, of whom 41 were men and 77 were women. Both rheumatoid arthritis and psoriasis are more common in women, and these figures do not differ significantly from the sex incidence in other series of patients with psoriasis or rheumatoid arthritis above [*14,25*]. Clinically the patients fell into three groups. In the first group twenty-two had classic "psoriatic arthropathy" with primarily distal joint involvement and nail changes of the same digits ("distal joint arthritis"). They had a negative S.C.A.T. Of the second group, ten had severely deforming arthritis due to ankylosis and disorganization of many joints ("deforming arthritis"); four had typical arthritis mutilans. All had a negative S.C.A.T. In the third group eighty-six had an arthritis clinically indistinguishable from rheumatoid arthritis. Sixty-

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six of these had a negative S.C.A.T. and they are considered as a separate entity ("indistinguishable arthritis"). In twenty the S.C.A.T. was positive and it is thought that they are examples of coincidental rheumatoid arthritis.

ONSET OF THE ARTHRITIS

The age at onset of arthritis in patients with uncomplicated rheumatoid arthritis did not differ significantly from the results obtained by the Empire Rheumatism Council Survey of 532 patients [*11*]. The distribution of age at onset among patients with psoriasis and erosive arthritis differed from those with uncomplicated rheumatoid arthritis in that there were significantly more patients with deforming arthritis which began under thirty years of age (70 per cent), and fewer patients with indistinguishable arthritis had an onset in the sixth decade (8 per cent).

The average age at onset of arthritis in patients with psoriasis and coincidental rheumatoid arthritis was the same as that in the Empire Rheumatism Council Survey. (Table I.) Indistinguishable arthritis began at a significantly earlier age than coincidental rheumatoid arthritis ($P < 0.02$), as did deforming arthritis ($P < 0.01$).

It was not always easy to be certain of the acuteness of onset from the history, but as far as could be ascertained the only significant difference in the acuteness of onset was that distal joint arthritis was more often insidious in onset.

Thirty-five per cent of patients with uncomplicated rheumatoid arthritis (25 per cent among the men, 40 per cent among the women) experienced constitutional disturbances at the onset of the arthritis. This was less common in those with indistinguishable arthritis (19 per cent). The men with deforming arthritis had more constitutional disturbance than men with indistinguishable arthritis (75 per cent and 12 per cent). Pyrexia at the onset of the arthritis was more common in men with deforming arthritis (50 per cent) than in men with uncomplicated rheumatoid arthritis (6.2 per cent), a significant difference ($P < 0.02$). Infection preceded the arthritis in 0 to 9 per cent and there was no significant difference in any group.

A monarticular onset of the arthritis occurred in 39 per cent of patients with uncomplicated rheumatoid arthritis, an incidence similar in all groups. There was no significant difference in joints involved at the onset of arthritis except in the group with distal joint arthritis. The metacarpophalangeal, proximal interphalangeal and shoulder joints were most commonly affected initially; the metatarsophalangeal, wrist and knee joints were next in order of frequency. In the group with distal joint arthritis the distal interphalangeal joints were usually involved at the onset of the arthritis (59 per cent), a very highly significant difference from the other groups ($P < 0.001$).

TABLE I
AVERAGE AGE AT ONSET OF ARTHRITIS

Type of Arthritis	Average Age at Onset (yr.)		
	Males	Females	Total
Distal joint	36.3 ± 3.9	42.9 ± 4.1	39.6 ± 2.9
Deforming	23.7 ± 2.3	28.5 ± 5.2	26.6 ± 3.4
Coincidental rheumatoid	43.0 ± 3.9	42.3 ± 4.2	42.6 ± 2.4
Indistinguishable	35.7 ± 4.7	33.3 ± 1.9	33.9 ± 1.8
Rheumatoid (E.R.C. Survey, 1950)	41	42	41.5

COURSE OF THE ARTHRITIS

Although the distribution of affected joints was the same in all groups, individual joints were affected with different frequency. (Table II.) The shoulders, elbows, wrists, metacarpophalangeal and proximal interphalangeal joints were all more frequently involved in the group with uncomplicated rheumatoid arthritis than in the groups with indistinguishable and distal joint arthritis ($P < 0.01$). The hips were involved more often in the group with deforming arthritis than in the groups with uncomplicated rheumatoid arthritis and indistinguishable arthritis ($P < 0.01$). In the group with deforming arthritis four had typical arthritis mutilans. They showed classic "opera glass" hands, "main en lorgnette," and a similar condition of the feet. Radiographically there was melting away of the bones. (Fig. 1.) The other six of the group showed severe deformity due to ankylosis and disorganization of many joints. Four were unable to walk and the other two were very restricted in their activity. The greatest deformity possible in any type of arthritis occurred in these patients. The sacroiliac joints were involved radiographically in six. In the group with distal joint arthritis the distal interphalangeal joints were most commonly involved and the evolution of such changes is shown in Figures 2A and

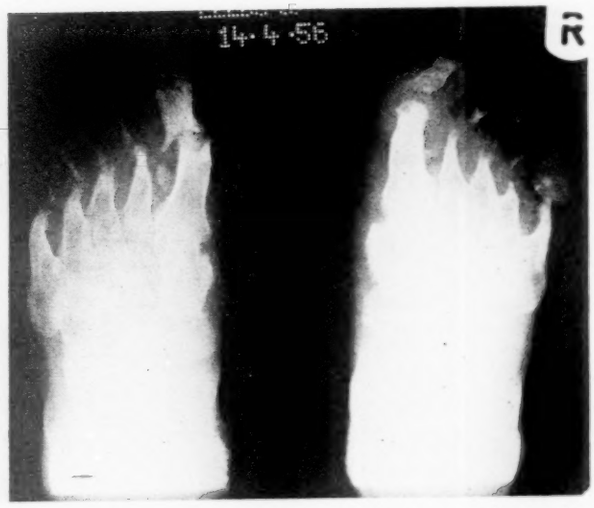


FIG. 1. Roentgenogram of the feet of a patient with psoriasis and arthritis mutilans. There is tapering of the metatarsal heads and complete disappearance of some phalanges.

2B. The arthritis was more often asymmetrical in this group (36.3 per cent) than in those with uncomplicated rheumatoid arthritis (5.2 per cent), a highly significant difference ($P < 0.01$). In only one patient was arthritis limited to the distal joints.

Barber [*2*] and Sherman [*37*] have commented that the clinical appearance of the joints in psoriatic arthritis may simulate gout. Such a similarity occurred in uncomplicated rheumatoid arthritis (17.8 per cent) and was present with significantly greater frequency (50 per cent) only in the group with distal joint arthritis ($P < 0.01$). This difference was probably significant among the women ($P < 0.05$) but more definitely so among the men ($P < 0.02$).

It has been stated [*37*] that during exacerbations of psoriatic arthritis many patients have severe transient migratory aches and pains in several joints, particularly the spine. Migratory pains were not found any more frequently in patients with psoriasis and arthritis than in those with uncomplicated rheumatoid arthritis.

Rheumatoid arthritis coincidental with psoriasis exhibited no features which differed from uncomplicated rheumatoid arthritis. This was the only group of patients with psoriasis in whom subcutaneous nodules were found (20 per cent), an incidence similar to that of uncomplicated rheumatoid arthritis (27 per cent). Extensor tendon sheath effusions were found with similar frequency in both these groups (20 per cent), and such effusions were present

TABLE II

PERCENTAGE OF JOINTS INVOLVED IN VARIOUS TYPES OF ARTHRITIS

Type of Arthritis	No. of Patients	Acromio-clavicular	Sterno-clavicular	Shoulder	Elbow	Wrist	Meta-carpo-phalan-geal	Proximal Inter-phalan-geal	Cervical Spine	Hip	Knee	Ankle	Mid-tarsal	Meta-tarso-phalan-geal
Distal joint	22	17	. .	18	23	23	36	50	9	. .	9	27	9	27
Deforming	10	30	30	80	80	100	80	90	70	20	80	60	50	80
Coincidental rheumatoid	20	25	20	40	50	70	75	75	20	5	45	55	15	75
Indistinguishable	66	15	12	36	26	32	42	56	26	7	33	27	14	42
Uncomplicated rheumatoid	95	21	13	52	66	78	86	88	20	5	60	68	13	61

TABLE III
PERCENTAGE OF FUNCTIONAL GRADE IN VARIOUS FORMS OF ARTHRITIS

Type of Arthritis	No. of Patients	Functional Grade				
		1	2	3	4	5
Distal joint	22	68	22	. .	. .	. .
Deforming	10	. .	. .	30	50	20
Coincidental rheumatoid	20	15	30	20	20	5
Indistinguishable	66	49	23	20	8	. .
Uncomplicated rheumatoid	95	17	33	39	10	1

more frequently in patients with uncomplicated rheumatoid arthritis than in those with indistinguishable arthritis (4.5 per cent; $P < 0.01$).

The arthritis was severe in the group with deforming arthritis, but in the groups with indistinguishable and distal joint arthritis it was less severe than in those with uncomplicated rheumatoid arthritis. Ulnar deviation was more common in patients with uncomplicated rheumatoid arthritis than in those with indistinguishable and distal joint arthritis, as was muscular wasting. These two features were more common in the group with deforming arthritis than in those with uncomplicated rheumatoid arthritis. At the time of examination the disability suffered by the patient throughout the course of the arthritis was graded as mild, moderate or severe, and the present functional grade assessed in categories defined by the Empire Rheumatism Council [*15*]. The patients with distal joint and indistinguishable arthritis experienced less disability than those with uncomplicated rheumatoid arthritis. This was reflected in the functional grading. (Table III.) Many more patients with distal joint and indistinguishable arthritis were in grade 1 than those with uncomplicated rheumatoid arthritis ($P < 0.01$). There was no significant difference between those with uncomplicated rheumatoid arthritis and those with rheumatoid arthritis and coincidental psoriasis ($P > 0.8$).

Each patient was asked to state whether the pain during the course of the arthritis had been mild, moderate or severe. Milder pain was experienced by the patients with distal joint arthritis than by those with indistinguishable or uncomplicated rheumatoid arthritis. Surprisingly, milder pain was also experienced by the patients with deforming arthritis than by those with indistinguishable or uncomplicated rheumatoid arthritis.

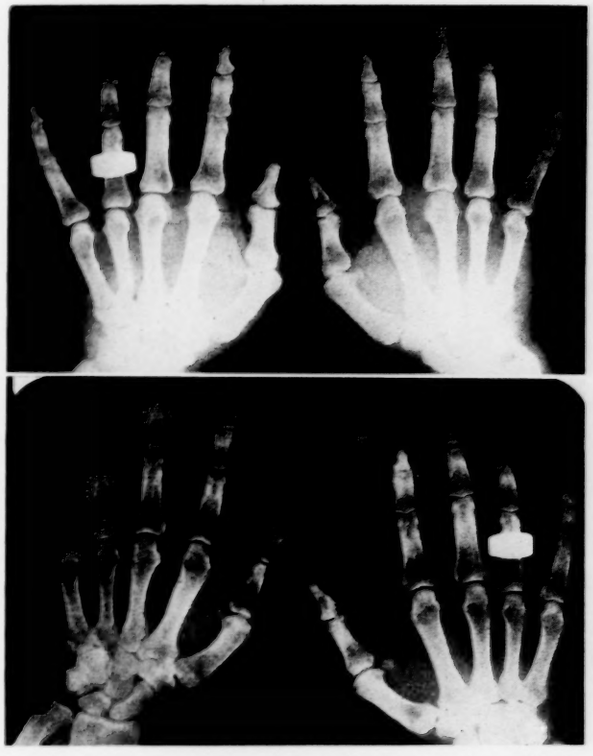


FIG. 2. Roentgenogram of hands in distal joint arthritis. *Top*, near onset. *Bottom*, two years later. The evolution of changes is best seen in the distal interphalangeal joints of the index and little fingers.

Subjectively the joints to be worst involved were most commonly the knees (30 per cent) in all patients except those with distal joint arthritis in whom the distal interphalangeal joints were often the worst involved (27 per cent). In patients with deforming arthritis, however, the cervical spine was listed as the worst involved site in 30 per cent, significantly more so than in patients with uncomplicated rheumatoid arthritis (6 per cent; $P < 0.01$).

RELATION OF PSORIASIS AND ARTHRITIS

In some ways joint changes seemed more closely related to lesions of the nails than to psoriasis of the skin. The nails were involved more often in patients with psoriasis and erosive arthritis (81 per cent) than in patients with uncomplicated psoriasis, in whom the incidence of nail changes was 32 per cent ($P < 0.01$). In 310 unselected patients with uncomplicated psoriasis, nail changes occurred in 18 per cent. The higher incidence in the present control



FIG. 3. Nail changes in psoriatic arthritis. A, pitting. B, discolouration in the distal part. C, hyperkeratosis of the thumb nails with arthritis of the distal joint. D, ridging.

group compared with the unselected series is probably due to the older age of the former. Since nail changes were almost as common in patients with coincidental rheumatoid arthritis as in those with psoriatic arthritis (Table IV) it may be that such changes are non-specific, occurring more frequently with any type of erosive arthritis. There seemed a more distinct relation in the group with distal joint arthritis however. Nail changes were invariably present in these patients and in two the nails only were involved. In eight there was a marked topographical association between nail and joint changes. Changes which occurred included pitting, discolouration, hyperkeratosis, subungual separation from the nail bed distally, and ridging. (Figs. 3A, 3B, 3C and 3D.) The fingers and toes were involved equally in all patients. Hyperkeratosis was the most common, discolouration and pitting next most common, and ridging least frequent. (Table IV.)

TABLE IV
PERCENTAGE OF TYPES OF NAIL CHANGES IN VARIOUS FORMS OF ARTHRITIS COMPARED WITH UNCOMPLICATED PSORIASIS

Type of Arthritis	No. of Patients	Nail Changes (%)			
		Present	Pitting	Hyperkeratosis	Ridging
Distal joint	22	100	41	100	41
Deforming	10	90	50	80	30
Coincidental rheumatoid	20	70	40	60	35
Indistinguishable	66	79	45	64	21
Uncomplicated psoriasis	85	32	22	24	22

Nail and joint changes were more commonly synchronous in onset than skin and joint changes (Fig. 4), the difference being highly significant ($P < 0.01$). It is of interest that of the patients with a negative S.C.A.T. the arthritis preceded the psoriasis in twenty-five. In the group with distal joint arthritis there was a synchronous onset of nail and distal interphalangeal joint changes in the majority of patients. (Fig. 5.) In this group a synchronous exacerbation of nail and joint condition (73 per cent) was twice as common as a synchronous exacerbation of skin and joint condition (36 per cent), a difference which is highly significant

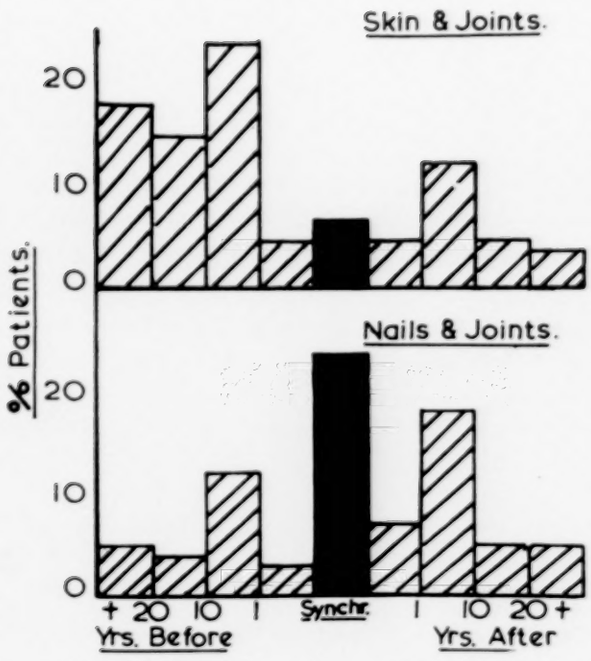


FIG. 4. Onset of arthritis in psoriatic arthritis related to the onset of skin and nail changes. A synchronous onset of nail and joint changes was more common than skin and joint changes.

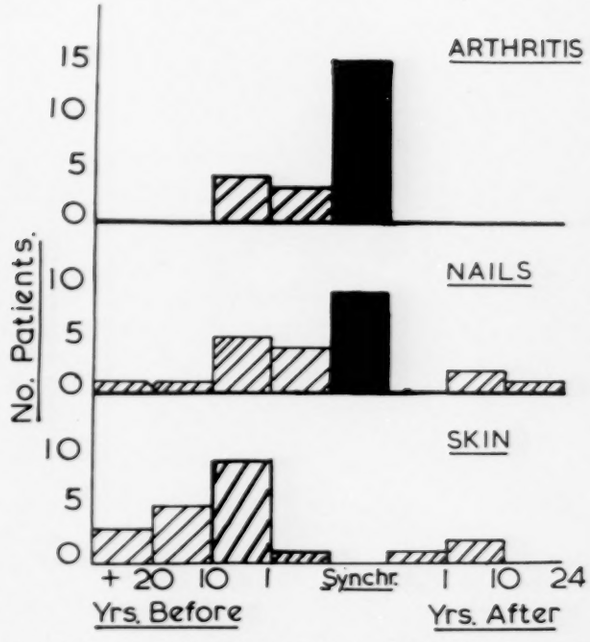


FIG. 5. Onset of distal interphalangeal joint involvement related to the onset of arthritis, nail and skin changes. Arthritis usually began in the distal joints, and distal joint changes were often synchronous in onset with nail changes, but never with skin changes.

($P < 0.01$). An inverse relation between activity of skin and joint lesions was seen as commonly as a synchronous exacerbation in all groups.

A family history was considered positive if the disease occurred in parents or siblings. A family history of psoriasis was obtained in 33 per cent of the patients with uncomplicated psoriasis. No significant difference was observed in the groups with psoriasis and arthritis, but all these groups differed markedly ($P < 0.01$) from uncomplicated rheumatoid arthritis in which a family history was present in 2 per cent. (Table v.) A family history of rheumatoid arthritis was more common in patients with uncomplicated rheumatoid arthritis than in those with uncomplicated psoriasis ($P < 0.01$). There was no significant difference in the frequency of such a family history between the patients with uncomplicated rheumatoid arthritis and those with psoriasis and arthritis. These findings are difficult to evaluate because of the small figures in some of the groups, the fact that the diagnosis of the type of arthritis depended on the patient's story, and the inability to correlate it with results of the S.C.A.T. of serum from relatives. It is of interest that a family history of psoriatic arthritis was most common in the group with deforming arthritis. There was no significant difference in the family history of other rheumatic complaints, except that a family history of rheumatic fever was obtained in a significantly higher proportion of the patients with indistinguishable arthritis than in those with uncomplicated rheumatoid arthritis ($P < 0.01$). This difference was not significant in the men (> 0.05) but was in the women ($P < 0.01$).

TREATMENT

The psoriasis was not usually resistant to treatment, contrary to some reports [*31,38*]. In none of the arthritic groups was there any significant difference in the proportion of patients with psoriasis resistant to treatment compared with uncomplicated psoriasis ($P > 0.3$). Most patients with psoriasis were treated with the daily administration of dithranol, tar bath and ultra-violet light [*25*].

Many have recorded that the arthritis subsides with treatment of the psoriasis [*16,27,33*]. Experience in the present series was sharply at variance with this finding. In only 10 of the 118 patients was such a regression experienced. Often the psoriatic arthritis was sufficiently mild not to require treatment. When therapy was required a regimen was instituted similar to that for rheumatoid arthritis. Bed rest, salicylate therapy

TABLE V

PERCENTAGE FAMILY HISTORY OF RHEUMATIC COMPLAINTS AND PSORIASIS IN ALL GROUPS

Group	No. of Patients	Sex	Percentage of Family History					
			Psoriasis	Rheumatoid Arthritis	Osteoarthritis	Rheumatic Fever	Muscular Rheumatism	Psoriatic Arthritis
Distal joint	10	Male	50	10	18	10	30	..
	12	Female	50	17	20	17	58	8
	22	Total	50	14	..	17	45	4
Deformed	4	Male	25	..	..	..	..	25
	6	Female	50	..	33	17	17	33
	10	Total	40	..	20	10	10	30
Coincidental rheumatoid	9	Male	33	11	11	11	44	..
	11	Female	36	9	27	9	55	9
	20	Total	35	10	20	10	50	5
Indistinguishable	18	Male	28	11	11	11	28	6
	48	Female	23	12	19	27	27	6
	66	Total	24	12	17	23	27	6
Uncomplicated rheumatoid	32	Male	..	21	11	9	20	..
	63	Female	3	25	19	8	33	..
	95	Total	2	24	17	8	29	..
Uncomplicated psoriasis	24	Male	25	4	21	8	12	..
	61	Female	36	6	6	18	23	2
	85	Total	33	6	11	15	20	..

and appropriate physiotherapy were the first lines of attack. Twenty-eight patients were given cortisone or prednisolone, with short term improvement in the majority, although of four with distal joint arthritis only one improved. Intravenous corticotrophin [*5*] was given to twenty-five patients with temporary improvement in all except three.

Chrysotherapy was given to forty-eight psoriatic patients. Ragan and Tyson [*35*] found a poor response in eleven psoriatic patients, in four of whom toxic reactions developed. Graham [*19*] states that psoriatic patients are more sensitive to gold and that an exacerbation of the skin lesion may occur. Toxic reactions in the present series were no more frequent than in forty-two of the patients with uncomplicated rheumatoid arthritis who had received gold (7 per cent). A significantly larger proportion ($P < 0.01$) of patients with uncomplicated rheumatoid arthritis (85 per cent) improved to some extent on chrysotherapy than those with indistinguishable (63 per cent) and deforming arthritis (40 per cent), but no control trial was made.

COMMENTS

The development of the Rose-Waaler sheep cell agglutination test (S.C.A.T.) has proved a valuable objective aid in diagnosing rheumatoid arthritis [*1,22,29,36,43*]. From a previous study it was tentatively suggested that psoriatic arthritis was an entity distinct from rheumatoid arthritis [*44,45*]. The present investigation supports this suggestion. If psoriasis merely modified the rheumatoid arthritis and caused a negative S.C.A.T. one would expect all the patients to have a negative S.C.A.T. In fact a number had a positive reaction, as one would expect if psoriatic arthritis were a separate entity and other patients had psoriasis plus rheumatoid arthritis—the coincidence of two common diseases. This interpretation is strengthened by the finding of subcutaneous nodules in 20 per cent of the latter group. The incidence is similar to that in the control series of patients with uncomplicated rheumatoid arthritis, and corresponds with the figures of other authors [*1,3,39*]. Subcutaneous nodules are regarded by many as the most characteristic lesion of rheumatoid arthritis [*3,6*]. Furthermore the clinical features of coincidental rheumatoid arthritis differed in no way from uncomplicated rheumatoid arthritis.

It is incorrect therefore to label all patients with psoriasis and erosive arthritis as having psoriatic arthritis [*42*]. Nor is it necessary for the arthritis to follow long continued and uncontrolled psoriasis [*23*], for the joints to be relieved by treatment of the skin [*33*] or for the skin lesions and arthritic manifestations to be atypical [*11*].

There seems no justification for restricting the term to those patients in whom only the distal joints are involved [*4*], or to a peculiarly destructive form of arthritis associated with psoriasis [*17,40*]. Numerous authors have laid down as diagnostic criteria, synchronous remissions and relapses in arthritis and cutaneous manifestations [*16,27,28*]. This occurred in relatively few patients and the arthritis paralleled nail changes to a greater extent than skin changes.

It is suggested that the term psoriatic arthritis should be used for the disease of patients with psoriasis and erosive arthritis having a negative S.C.A.T. These may have an arthritis primarily involving the distal interphalangeal joints and closely related to nail changes. The arthritis then is usually insidious in onset, asymmetrical, relatively mild and often mistaken for gout. A severely deforming arthritis, sometimes progressing to arthritis mutilans, also occurs. It begins at a younger age, is often accompanied by constitutional disturbance at its onset, involves almost every joint in the body including the hips and sacroiliac joints, and often causes much discomfort from involvement of the cervical spine. Finally there is a group with an arthritis indistinguishable from rheumatoid arthritis on clinical examination, although the average age of onset is younger, fewer joints are involved, and it produces less disability. In some patients arthritis precedes psoriasis, and in a previous study [*44*] it was suggested from this observation that some patients with apparently uncomplicated rheumatoid arthritis but a negative S.C.A.T. are destined in later years to have psoriasis develop [*44*]. This has since been observed [*13,24*].

The failure to appreciate that psoriatic arthritis may manifest itself in these various forms has been responsible for contradictory reports in the literature. For instance, Sherman [*37*] in her review comments that the onset is usually monarticular whereas Jeghers and Robinson [*27*] maintain that it is polyarticular. In our experience the onset is more often monarticular in patients with distal joint arthritis which Sherman studied, but not in the other groups which were included in the series of Jeghers and Robinson. It was because Sherman confined her analysis to data on patients with distal joint arthritis that she observed the similarity to gout of many, but her lack of a control series of patients with uncomplicated rheumatoid arthritis would seem to invalidate her claim that patients with psoriatic arthritis are characterized by transient migratory pains particularly in the back. These pains were experienced as frequently by patients with rheumatoid arthritis. It is appreciated that the present control series has the defect, that while patients with psoriatic arthritis were from both dermatological and rheumatic clinics, the control series was obtained from one or the other. Matched series taken from the general population would have been more accurate had it been possible to obtain them. However the majority of patients with psoriatic arthritis had been to both clinics at some time during the course of the disease.

Treatment of one lesion did not influence the course of the other, contrary to the reports of some authors [*16,27,33*]. The arthritis and psoriasis should be treated each on its merits. While chrysotherapy did not produce any more toxic reactions in patients with psoriatic arthritis than in those with rheumatoid arthritis, it was not as effective in psoriatic arthritis as it was in rheumatoid arthritis.

SUMMARY

One hundred fifty-four patients with psoriasis and various rheumatic complaints have been studied. In patients without erosive arthritis there were no unusual features of the skin or joint condition, and their association seemed fortuitous. There were 118 patients with psoriasis and erosive arthritis. They were contrasted with ninety-five patients with uncomplicated rheumatoid arthritis and a positive response to a sheep cell agglutination test and eighty-five with uncomplicated psoriasis. Twenty patients had psoriasis, erosive arthritis and a positive response to a sheep cell agglutination test. They did not differ from patients with uncomplicated rheumatoid arthritis and are thought to be examples of coincidental rheumatoid arthritis and psoriasis.

Ninety-eight patients were thought to have psoriatic arthritis. The clinical features of this group have been analysed and compared. They were classified on clinical grounds into three groups (1) those with an arthritis involving primarily distal interphalangeal joints, (2) those with a severe deforming arthritis, (3) those with an arthritis clinically indistinguishable from rheumatoid arthritis.

Acknowledgment: I am indebted to Professor S. J. Hartfall for his help and encouragement in this study and to Dr. J. T. Ingram for placing

much clinical material at my disposal. My thanks are also due to Dr. A. G. S. Hill and Dr. D. S. Wilkinson with whom the initial work was done. Dr. J. Everall assessed the dermatological features of some of the patients.

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Seminar on Mycotic Infections

Aspergillosis*

A Review and Report of Twelve Cases

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ASPERGILLOSIS is caused by several different species of aspergillus; it is characterized by granulomatous, inflammatory or necrotizing lesions which may involve any tissue of the body. The lung is the most common site of significant infection. Aspergillosis varies in severity from an incidental, saprophytic relationship to a fulminating, fatal infection. The disease is found in all races throughout the world. It is more common in adults than children and in males than females [*1*]. Excellent reviews of aspergillosis were presented in 1928 by Wahl and Erickson [*2*] and in 1952 by Hinson, Moon and Plummer [*3*]. In recent years there have been a number of case reports indicating a relationship between the use of antimicrobials and steroid hormones and aspergillus infection.

This report presents clinical and pathological data from twelve cases of aspergillosis seen at the authors' institutions in the past six years, eleven within the past four years. Eleven of these twelve cases were associated with the use of antibiotics or sulfonamides; other possible predisposing factors were debilitating illness, use of adrenocortical steroids and corticotropin, leukopenia, radiation, use of anti-neoplastic drugs and recent surgery. Cases of aspergillosis in the literature in which antibacterial chemotherapy or steroid therapy may have played a role are summarized in tabular form. A new classification of aspergillosis is proposed.

CASE REPORTS

CASE I. M. C., a seventy-four year old white man, was admitted to the Wadsworth Veterans Hospital in 1953 complaining of rectal pain. Two years previously he had had x-ray therapy for squamous cell carcinoma of the anus. Following preparation of the bowel with sulfasuxidine and oxytetracycline, a combined abdominoperineal resection was performed. The urethra was inadvertently entered during the difficult dissection, requiring an indwelling catheter. After one week of postoperative penicillin and streptomycin therapy chills and fever developed. An infiltration was present in the right lung. With sulfisoxazole therapy the temperature promptly became normal. A urethrocutaneous fistula developed shortly thereafter, with high daily fever. The patient's condition gradually deteriorated, and on the sixtieth postoperative day nausea, vomiting and diarrhea developed; he went into shock and died.

Autopsy showed necrotizing pseudomembranous colitis, acute fibrinous pericarditis, chronic prostatitis and seminal vesiculitis, and extensive bilateral bronchopneumonia with abscess cavities in the upper lobes. Microscopically, in addition to the acute bronchopneumonia and organized and organizing pneumonitis, the cavities were lined by fibrin and patchy granulation tissue with some Langhans-type giant cells. In the amorphous granular debris in the cavities there were stellate masses of large, irregular septate hyphae consistent with aspergillus, with focal invasion of the cavity wall. A small vessel showed invasion of the vascular wall. Cultures were not taken.

Comment: This example of invasive secondary aspergillosis was manifested as multiple small pulmonary abscesses in an acute bronchopneumonia. Predisposing factors included recent surgery for carcinoma of the anus and extensive antibacterial therapy with both antibiotics and sulfonamides.

CASE II. J. G., a sixty-two year old white man, entered the Wadsworth Veterans Hospital in 1954 for evaluation of an anemia intermittently present for ten years. There was a history of exposure to benzene, ethyl acetate and butyl acetate. The patient was pale,

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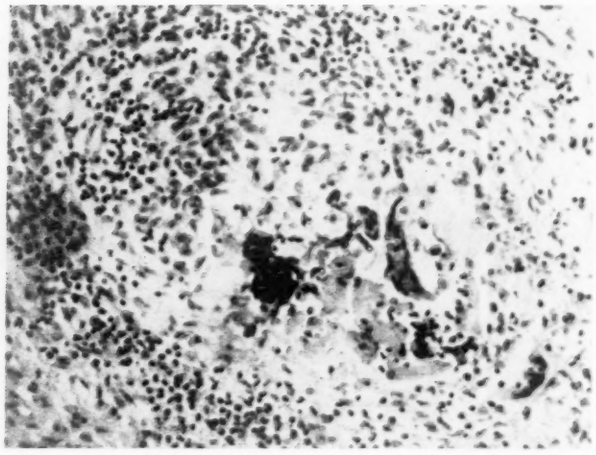


FIG. 1. Case III. Photomicrograph showing a small granuloma surrounding a group of fungi. Some hyphae can be seen in giant cells.

with many petechiae, retinal hemorrhages and inspiratory wheezes in both lungs. Laboratory studies showed a hemoglobin of 9.5 gm. per 100 ml., a leukocyte count of 1,800 per cu. mm. with 87 per cent lymphocytes and 119,000 platelets per cu. mm. The bone marrow was hypoplastic and erythrocyte survival time was one-third of normal. There was a right hilar mass. Following treatment on an outpatient basis with multiple transfusions, he was readmitted for a trial of cortisone therapy (300 mg. administered daily). After one week, fever and productive cough appeared which did not respond to penicillin or tetracycline. He died two days later. Staphylococcus aureus was cultured from the sputum.

Autopsy showed extensive patchy bronchopneumonia with consolidation and a pleomorphic epidermoid carcinoma of the right lung involving mediastinal nodes. In an area of acute necrotizing bronchitis there was a superimposed infection by organisms consistent with aspergillus. Elsewhere a chronic esophagitis and bronchitis due to candida was noted. The bone marrow showed erythroid hypoplasia, leukocytic maturation arrest and diminished megakaryocytes.

Comment: This case of localized secondary aspergillosis occurred in a patient with refractory anemia and profound leukopenia complicated by bronchogenic carcinoma. A fatal staphylococcal pneumonia developed during cortisone therapy, and antibiotics were used briefly.

CASE III. G. L., a thirty year old white man, was admitted to the Wadsworth Veterans Hospital in 1954 complaining of back and chest pains of one week's duration, and numbness and weakness of the lower extremities dating from a lumbar puncture two weeks prior to admission. Physical examination showed slight hepatosplenomegaly, hyperactive deep tendon reflexes in the lower extremities, bilateral ankle clonus and positive Babinski signs. Hematologic studies revealed the presence of acute myeloblastic leukemia. After a sudden increase in pain with flaccid hemiplegia at the level of T-6, surgical decompression revealed a hemorrhagic extradural mass infiltrated by leukemic cells. Paraplegia remained and an indwelling catheter was required. Recurrent infections of the urinary tract necessitated sulfonamide and antibiotic therapy. Cortisone and amethopterin treatment resulted in a transient leukemic remission. Terminally, bleeding developed and the patient died with evidence of bilateral bronchopneumonia three and a half months after admission.

Autopsy showed acute myelogenous leukemia, extensive hemorrhagic and gangrenous cystitis, prostatitis and epididymitis, chronic pyelonephritis and acute hemorrhagic bronchopneumonia. Organisms consistent with aspergillus were present in small granulomas in the lungs within multinucleated giant cells. (Fig. 1.)

Comment: This is an example of localized secondary aspergillosis in the form of pulmonary granulomas. Predisposing factors included acute leukemia and bronchopneumonia, with prolonged treatment incorporating cortisone, sulfonamides, antibiotics, amethopterin and surgery.

CASE IV. J. H., a seventy-eight year old white man, was admitted to the Wadsworth Veterans Hospital in 1955 with an intertrochanteric fracture of the right hip. An open reduction with internal fixation was followed by an unexplained fever which responded gradually to the administration of tetracycline, penicillin and streptomycin. (Fig. 2.) One month later a volvulus required resection of a large segment of gangrenous bowel. A bilateral staphylococcal parotitis occurred postoperatively which was treated with x-ray, antibiotics and surgical drainage. However, a staphylococcic bacteremia followed. This responded initially to the administration of tetracycline, ACTH and hydrocortisone; a relapse was treated with other antibiotics. Four days before the patient's death dehiscence of the abdominal wound with evisceration occurred, which was repaired under local anesthesia. His condition deteriorated rapidly and he died suddenly on the sixtieth hospital day. Three blood cultures on the last day contained coagulase-positive staphylococci.

The chief autopsy findings were bilateral necrotizing parotitis, bilateral acute bronchopneumonia, cystitis and arteriosclerotic heart disease. An abscess in the right lung, 1.5 cm. in size, was lined with fibrin and acute inflammatory cells, and contained a mass of branching hyphae consistent with aspergillus. Some

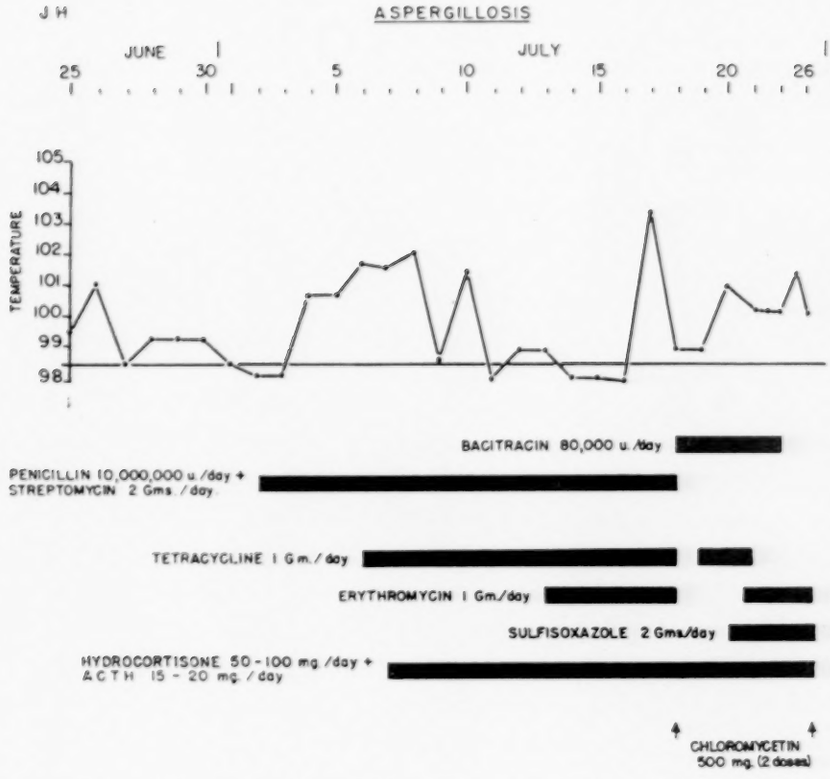


FIG. 2. The clinical course and therapy in Case IV.

filaments were noted to invade the wall of a blood vessel.

Comment: This patient had invasive secondary aspergillosis in the form of a small mycetoma with involvement of the blood vessels. Predisposing factors included debility from multiple causes, surgery and prolonged treatment with ACTH, hydrocortisone, a sulfonamide and several antibiotics.

CASE V. J. K., a thirty-five year old man with a brief history of fever and weight loss, was admitted to the Wadsworth Veterans Hospital in 1953 with a diagnosis of chronic myelogenous leukemia. He had generalized lymphadenopathy and hepatosplenomegaly. The hemoglobin was 9.5 gm. per cent, the leukocyte count was 270,000 per cu. mm., predominantly neutrophils. Radiation of the spleen produced improvement. During the following two years, relapses were treated with additional radiation and the administration of Myleran.® On his last admission in 1955 he was anemic and febrile. Radiation therapy resulted in a leukopenia of 500 cells per cu. mm. with 65 per cent basophils; this lasted four weeks, gradually changing to a leucocytosis prior to death. Febrile episodes did not respond to long courses of tetracycline and erythromycin. Further therapy with Myleran and cortisone failed and the patient died of bronchopneumonia.

Diffuse myelofibrosis was present at autopsy, in addition to granulocytic leukemia. There was an organizing pneumonitis and a focal necrotizing pneumonia which contained aspergilli. An esophageal ulceration was not sectioned and may have represented either candida or aspergillus infection.

Comment: This case illustrates the occurrence of invasive secondary pulmonary aspergillosis in a patient predisposed by chronic leukemia, pneumonitis, agranulocytosis and therapy with antibiotics and cortisone. Radiation and Myleran therapy also may have played a role.

CASE VI. A. R., a fifty-eight year old white man, was admitted to the Wadsworth Veterans Hospital in 1955 with severe headaches and vomiting. He previously had had bilateral iliac vein thrombosis with multiple pulmonary emboli. Evidence of a left frontotemporal lesion was present and, at craniotomy, a metastatic adenocarcinoma of the dura was found; decompression was carried out. Further studies were indicative of a primary bronchogenic carcinoma of the left lung. The patient's condition gradually de-

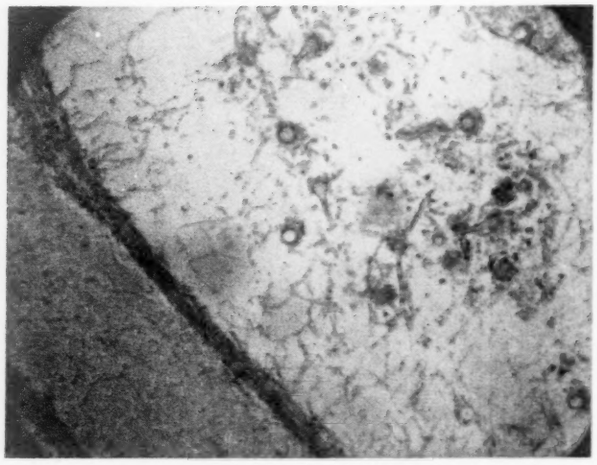


FIG. 3. Case VII. Photomicrograph showing aspergillus with recognizable conidiophores within an abscess cavity. Note the invasion of the abscess wall.

teriorated and he became confused and semicomatose; he died seven months after his last admission. Several courses of penicillin, alone or combined with streptomycin, were given during the course of his illness.

A left bronchiolar carcinoma with widespread metastases was found at autopsy. There were multiple old pulmonary emboli with infarctions, emphysema, bronchiectasis and organizing pneumonitis. A loculated, thin walled, pulmonary abscess cavity, 7.0 cm. in size, located at the margin of the carcinoma, contained a large clump of matted septate hyphae, consistent morphologically with aspergillus, and also many small masses of cocci.

Comment: This man with chronic pulmonary disease and bronchiolar carcinoma had received penicillin and streptomycin before death. Autopsy revealed localized secondary pulmonary aspergillosis in the form of an abscess cavity in close proximity to the carcinoma.

CASE VII. H. M., a fifty-eight year old white man, was initially admitted to the UCLA Medical Center in 1957 with fever and malaise. Five years previously he had had a left pneumonectomy for adenocarcinoma. A diagnosis of Hodgkin's disease had been made three years previously on the basis of a cervical lymph node biopsy. He had generalized lymphadenopathy, hepatomegaly, a hemoglobin of 8.7 gm. per cent and moderate neutropenia. He responded initially to the administration of nitrogen mustard, but subsequently fever, anemia, maxillary sinusitis, diarrhea and periods of severe neutropenia developed. On his second admission prednisolone therapy was begun and this was continued until his death. Intensive tetracycline treatment was given; erythromycin and nystatin also were used during the last two weeks of life. He also received Leukeran® for three weeks.

At autopsy the left lung was absent. The right lung contained many small gray-white nodules in the upper lobe and numerous cyst-like cavities lined by a gray-green powdery substance resembling, in all respects, the subsequent growth of fungi on laboratory media. Microscopically, the nodules and cavity walls contained abundant hyphae; many conidiophores recognizable as aspergillus lined the cavities. (Fig. 3.) The organism was identified on culture as A. fumigatus.

Comment: This man showed invasive secondary aspergillosis (bronchopneumonia) with many small cavities containing A. fumigatus. The recognition of typical conidiophores in tissue sections is uncommon. Predisposing factors were Hodgkin's disease and leukopenia, with prednisolone, Leukeran and antibiotic therapy.

CASE VIII. W. E., a sixty-eight year old man, was admitted to the UCLA Medical Center in 1957 with a two-week history of pain in the left side of the chest, cough and fever which progressed despite penicillin therapy. A past history of hypertensive cardiovascular disease, chronic congestive failure and emphysema was elicited. On admission, there was evidence of consolidation of the upper lobe of the left lung, and a leukocytosis with a shift to the left. Sputum cultures yielded coagulase-positive Staph. aureus, a klebsiella-aerobacter species and Escherichia coli. His hospital course is illustrated in Figure 4. Selected chest roentgenograms are illustrated in Figure 5. Despite intensive antibiotic therapy, a large cavity appeared in the upper lobe of the left lung. During several months of antibiotic and sulfonamide treatment, the cavity became smaller and was gradually filled with an enlarging mass. Bronchoscopy following a sudden hemoptysis disclosed no bleeding point, but washings yielded A. fumigatus on culture. A left upper lobectomy was performed; this was complicated by severe blood loss and contamination of the pleural space by the friable unattached intracavitary mass. The patient's postoperative course was marked by episodes of hypotension and anoxia. He was improving gradually when he died suddenly two weeks later.

The resected specimen consisted of necrotic lung with a large abscess cavity which contained a free mass of dense filamentous septate hyphae. Cultures of this material yielded A. fumigatus. At autopsy no further evidence of aspergillosis was noted. There was an extensive old posterior myocardial infarction mild pulmonary edema and emphysema.

Comment: This patient had acute necrotizing bacterial pneumonia with abscess formation.

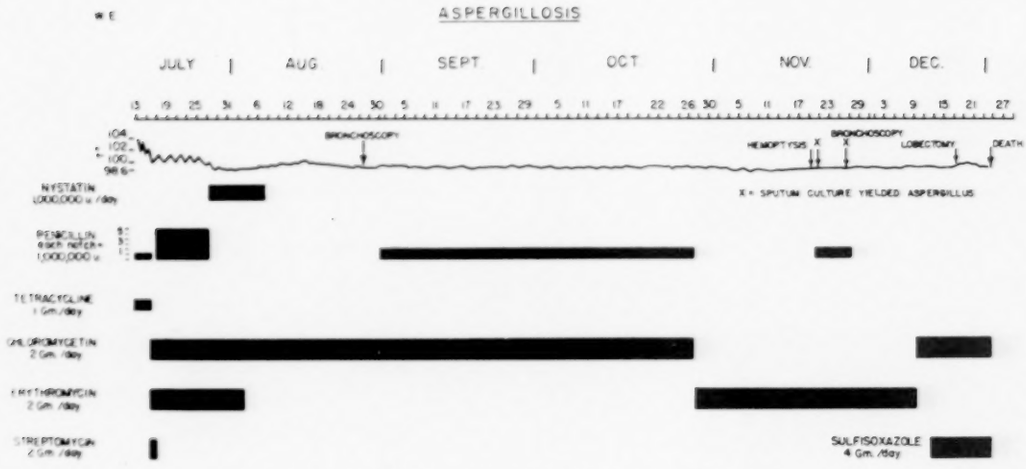


FIG. 4. The clinical course and therapy in Case VIII.

Long-term antibiotic and sulfonamide therapy was associated with secondary infection by A. fumigatus in the form of an intracavitary mycetoma.

CASE IX. H. V., a thirty-three year old woman, entered another hospital in 1958 following the acute onset of chills and fever. Twenty-four hours after expelling a macerated fetus she was found to be in shock and was treated with norepinephrine and dilatation and curettage. A blood transfusion, which had been started at the same time, was stopped after 200 ml. had been infused because of an apparent reaction. Following these procedures she became markedly oliguric and was transferred to the UCLA Medical Center. On examination, she was acutely ill and had slight icterus, bilateral flank tenderness and a slightly enlarged, tender uterus with a bloody discharge. She had a hemoglobin of 11.4 gm. per 100 ml., a leukocyte count of 45,250 per cu. mm. and a blood urea nitrogen of 36 mg. per 100 ml. She remained oliguric, with increasing azotemia and acidosis. The



FIG. 5. Case VIII. Two roentgenograms show a mycetoma in the upper lobe of the left lung; a detailed view of this is shown in the planigram which reveals the crescentic radiolucency surrounding the fungus ball.

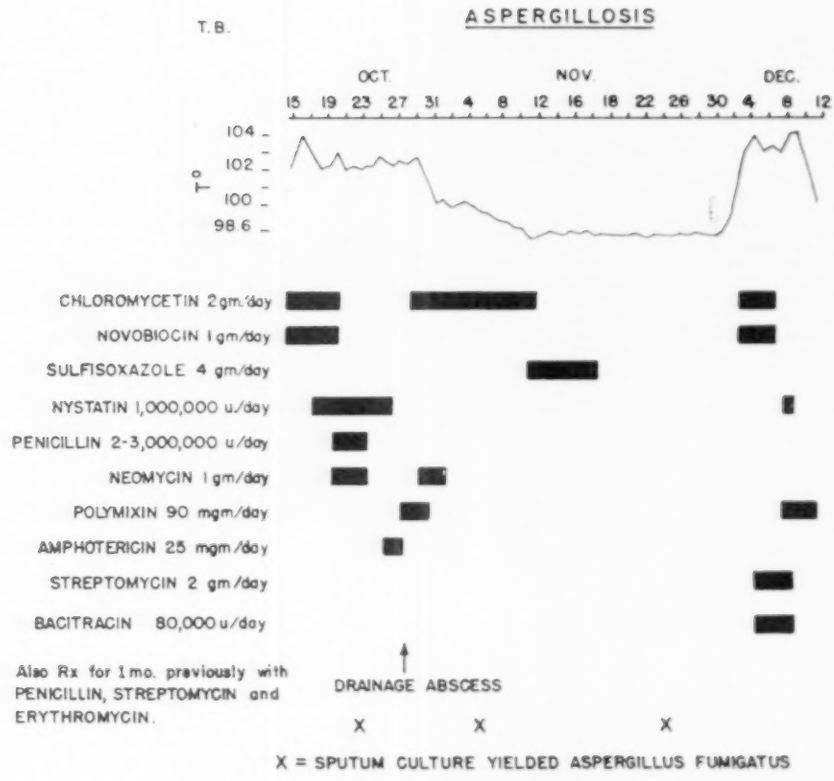


FIG. 6. The clinical course and therapy in Case x.

course was transiently improved by treatment with the artificial kidney and two peritoneal dialyses. She was intermittently febrile throughout her hospital course and was treated with intravenous chloramphenicol, erythromycin and penicillin. She died on the fifty-first hospital day.

Necropsy revealed a well developed, well nourished woman. There were many cutaneous petechiae. The lungs contained numerous grayish white nodules up to 4 cm. in diameter. Small similar gray areas were found in the myocardium. There were many small hemorrhagic and necrotic foci in the brain. The endometrial surface of the uterus was necrotic. Sections of the heart, lungs, spleen, brain and uterus showed large numbers of filamentous septate hyphae in areas of acute inflammation, necrosis and hemorrhage. Numerous vessels in these foci showed intraluminal hyphae invading the vascular walls and surrounding tissue. A. fumigatus was isolated from the uterus, brain and lung tissue.

Comment: This young woman had a septic abortion and a transfusion reaction followed by renal failure, which was unsuccessfully treated by dialysis. Death occurred from sepsis, and necropsy revealed A. fumigatus in the lung, uterus and brain. Hyphae were also seen in the heart and spleen. It is probable that the fungus infection occurred after the initial abortion, as slides of the initial curettings were reviewed and no fungus elements were seen. This is an example of disseminated, secondary aspergillosis.

CASE X. T. B., a forty-seven year old physician with chronic lymphatic leukemia was admitted to the UCLA Medical Center following an upper respiratory infection of one month's duration which had proved refractory to the administration of a variety of antibiotics. On examination he was febrile, with moderate dyspnea and cough. There were rales at both bases and hepatosplenomegaly. He had a hemoglobin of 12.9 gm. per 100 ml. and a leukocyte count of 220,000 per cu. mm. with 99 per cent lymphocytes. Proteus mirabilis and Streptococcus zymogenes were cultured from the sputum. The patient had a fluctuating course, as shown in Figure 6. An area of infiltration in the left lung did not respond to antibiotic treatment. A. fumigatus was cultured from the sputum on three separate occasions. His blood picture improved on Leukeran therapy but he suddenly went into shock and died on the fifty-seventh hospital day.

Necropsy revealed chronic lymphatic leukemia involving the spleen, liver, lymph nodes and bone marrow, with marked hepatosplenomegaly. In an area of organizing pneumonitis in the upper lobe

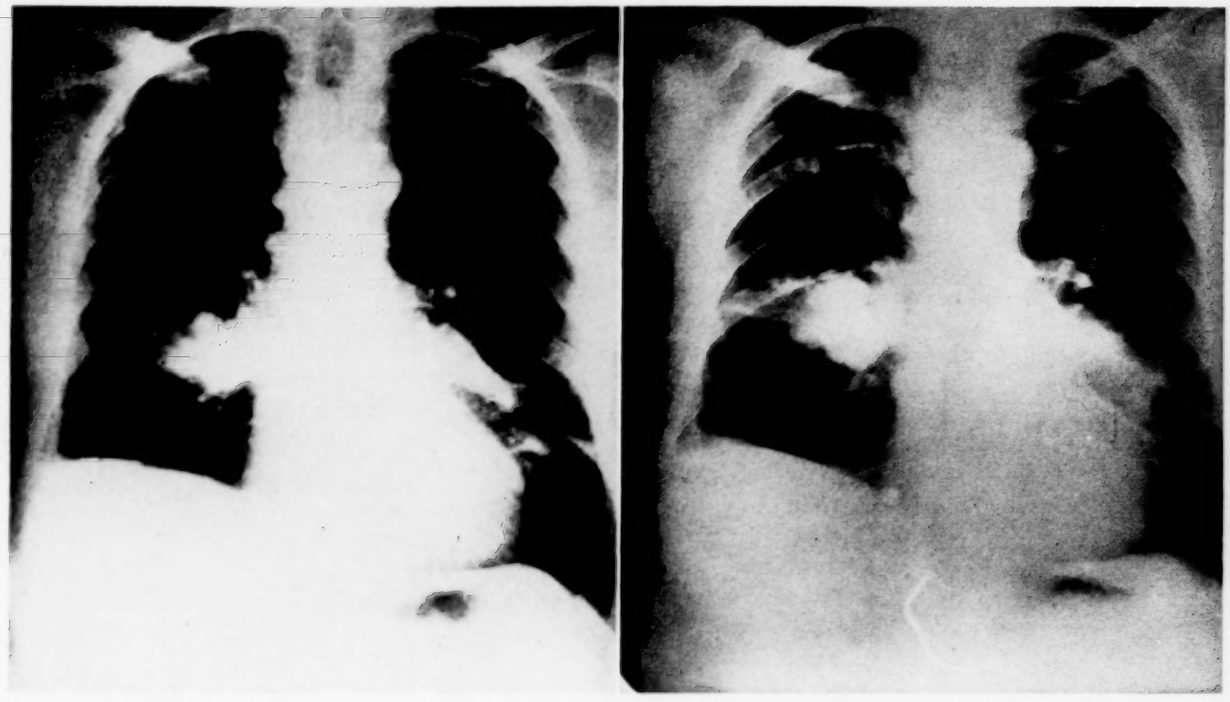


FIG. 7. Case XII. Posteroanterior views of the chest show parahilar infiltrate bilaterally and a small infiltrate in the right first anterior interspace. Progression is shown between the films of November 13, 1958 and January 15, 1959.

of the left lung there was a small cystic space lined by necrotic tissue and small granulomatous areas with giant cells. Septate hyphal fragments were present in several giant cells. Cultures of several lung fragments failed to grow fungi.

Comment: In this patient with chronic lymphatic leukemia an area of superimposed pulmonary infection contained organisms histologically consistent with aspergillus. Although autopsy cultures were negative, A. fumigatus had been cultivated on several occasions from sputum. He had received intensive antibacterial therapy over long periods and had been treated with Leukeran. This is an example of localized secondary aspergillosis.

In the original pathological study of this patient the aspergilli were not seen. We had originally intended using this patient to illustrate the difficulties in establishing a diagnosis with only positive cultures as evidence. When the lung sections were reviewed with this in mind the organisms were seen. This case also demonstrates how positive histological evidence may be overlooked.

CASE XI. F. K., a thirty-nine year old man, had had severe pneumonia in 1953 followed by a persistent productive cough and progressive dyspnea. Since his original illness he had been hospitalized ten times for pneumonia and chronic lung disease. He was admitted to the UCLA Medical Center in 1958. Physical examination revealed a dyspneic and orthopneic man with a cough productive of yellowish green sputum. There was cyanosis of the lips and mucous membranes, venous distention, edema of the ankles and marked clubbing. Breath sounds were prolonged, with scattered rales throughout the lung fields. Laboratory examination revealed a hemoglobin of 19.1 gm. per 100 ml., leukocytes 6,100 per cu. mm. and a heavy growth of Pseudomonas aeruginosa in the sputum. Pulmonary function data showed a combined restrictive and obstructive ventilatory insufficiency, with an arterial oxygen saturation of 74 per cent. A chest roentgenogram showed far advanced pulmonary fibrosis. The electrocardiogram was compatible with chronic cor pulmonale.

The patient was treated with antibiotics, drainage, digitalis and diuretics. Prednisolone was added after one week. Two weeks later, after initial improvement in his cough and sputum production, his symptoms again became pronounced, and A. fumigatus was cultured from his sputum on two occasions. A six-day course of amphotericin B was given, without change in his clinical status. Three additional cultures, one before and two after amphotericin therapy, were overgrown by pseudomonas. The patient was discharged to be followed up in the Outpatient Department. Five months later the patient entered another hospital in cardiopulmonary failure and died.

TABLE I
CLASSIFICATION OF ASPERGILLOSIS

I. Primary aspergillosis—in the absence of underlying disease or other predisposing factors
- A. Localized
  - 1. Abscesses or granulomas (including mycetoma)
  - 2. Allergic—bronchitis with asthma and/or eosinophilia
- B. Invasive
  - 1. Acute—usually bronchopneumonic
  - 2. Chronic granulomatous disease—usually pulmonary
- C. Disseminated—widespread abscesses or granulomas

II. Secondary aspergillosis—associated with a local process, debilitating illness, impaired host defenses, or complicating antibacterial and/or steroid hormone therapy
- A. Localized—usually pulmonary
  - 1. Saprophytic relationship
    - a. Abscess (or mycetoma)
    - b. Focal infiltration
  - 2. Chronic, low grade infection or granuloma
- B. Invasive—usually bronchopneumonic
- C. Disseminated
  - 1. Endocarditis
  - 2. Multiple abscesses or granulomas (in the absence of endocarditis)

Multiple sections of lung obtained at autopsy were reviewed and showed severe bronchiectasis and pulmonary fibrosis with organized pneumonitis and superimposed acute bronchopneumonia and recent hemorrhages. No aspergilli were identified and cultures were not made at autopsy.

Comment: Antibiotics and adrenocortical steroids were given to this man for bronchiectasis and pulmonary fibrosis, and were associated with the emergence of A. fumigatus in his sputum. Amphotericin B was given empirically for a short period, but its effects on the aspergillus could not be adequately evaluated.

This case demonstrates the difficulty in making a definitive diagnosis of pulmonary aspergillosis. The presence of aspergillus in the sputum on two occasions, in the presence of bronchiectasis with antibiotic and steroid therapy, seemed to offer sufficient evidence of secondary fungus infection. However, the failure to find the organisms in autopsy material leaves the diagnosis in doubt.

CASE XII. B. B., a sixty-seven year old white man, was admitted to Wadsworth Veterans Hospital in 1958 complaining of cough, night sweats and a 25-pound weight loss of three months' duration. Two years previously a routine annual chest roentgenogram was reported to him as showing "spots on the lung." He remained asymptomatic until the present illness. The patient worked around grains and grain milling dust for many years and raised pheasants for two years, feeding the birds from sacks of mixed grain. The patient had received no steroid or antibacterial therapy.

Physical examination revealed no abnormalities except for evidence of recent weight loss. The hematologic examination was within normal limits except for a moderate anemia and a sedimentation rate of 30 mm. per hour. Chest roentgenograms showed densities in the right hilum extending into the mid-lung field, the lower left lung field and the right first interspace. (Fig. 7.) The initial impression was bronchogenic carcinoma with metastasis. Review of previous chest films showed the three pulmonary lesions noted on this admission to have been present two years before. On bronchoscopy, a small soft tissue mass was noted projecting from the lateral wall of the lower right lobe bronchus. Biopsy of this mass revealed hyphal elements consistent with aspergillus and a culture was identified as A. flavus.

The patient has received 2 gm. of griseofulvin* orally per day for four weeks without evidence of improvement.

Comment: This is an example of primary invasive aspergillosis of the chronic granulomatus variety occurring in a patient exposed to grain and grain dust, who had no underlying disease and who had not received steroids or antibiotics.

COMMENTS

Classification. A new classification of aspergillosis is presented in Table I. The disease has been divided into a primary variety which arises without the presence of an antecedent disorder and a secondary type which is always associated with an underlying local process, debilitating illness, or antibiotic or steroid therapy. Both of these varieties have been further subdivided into localized, invasive or disseminated, depending upon the type and extent of the inflammatory process.

Primary Aspergillosis. Localized, primary aspergillosis is seen primarily in the lung in the form of an abscess, mycetoma [*1*] or granuloma. However, other sites may be involved with similar, non-invasive processes; these include the external ear, skin, nails, nasal sinuses, eye, orbit, nasopharynx, vagina, urethra, pleural cavity, bronchial tree and brain [*1,3,5–8*].

Also included as localized, primary aspergillosis is the allergic variety of Hinson, Moon and Plummer [*3*]. The lesions in this instance are confined to the bronchial tree, at times with the

* Kindly supplied by Dr. G. Hildick-Smith of Johnson and Johnson, Inc., New Brunswick, New Jersey.

clinical picture of Loeffler's syndrome. The basic pathophysiology apparently is sensitization to the fungus, leading to production of an exudate in the bronchial lumen consisting of mycelium, mucus, fibrin, eosinophils, Curschmann's spirals and Charcot-Leyden crystals. This mass leads to bronchial blockage and subsequent collapse or consolidation. Typically there is a marked peripheral eosinophilia, and there may be asthma. One of the patients described by Hinson, Moon and Plummer [3] died in status asthmaticus. There are characteristically recurrent episodes of fever, severe cough and purulent sputum containing white or brownish flecks (of mycelium) just visible to the naked eye. Plugs may be expectorated, with subsequent improvement clinically and radiologically (suggesting unblocking of a bronchus). X-ray findings often persist for weeks; the appearance of new shadows in different locations in association with new episodes of clinical illness is common.

Invasive, primary aspergillosis usually takes the form of a pneumonia, with or without abscess formation [9], which may be fulminating and fatal [10]. Besides the lung, the brain may be involved by extension from the orbit [11] and sinuses [12].

In addition to acute pneumonic aspergillosis, a chronic granulomatous lung disease occurs which closely simulates pulmonary tuberculosis. This variety is usually an occupational illness of workers exposed to cereal grains. Symptoms include cough, hemoptysis, pleurisy, fever and weight loss. Patients may cough up black or dark granules resembling soot or coal dust which actually represent dislodged conidia [13]. Healing may lead to progressive fibrosis [14]. One of our patients (Case XII) belongs in this category.

Disseminated, primary aspergillosis apparently is rare. Involvement of the lung, tongue, palate and mesenteric nodes was reported by Wheaton [15]. Peet described a patient with pulmonary involvement for seven years and eventual extensive spread to the cerebellum [16]. Hertzog, Smith and Goblin [10] cited a personal communication from Doub discussing a family of five with diffuse miliary lesions throughout both lungs.

Secondary Aspergillosis. Localized secondary aspergillosis is usually found in the lung, and is associated with some previous disease of local tissue, such as pneumonia (Cases I, II, III, IV, V, VIII and X), lung abscess (Case VIII), carcinoma of the lung (Case VI), pulmonary infarct [3], tuberculosis [17,18], pneumonoconiosis [19], lung cyst [3,20], bronchiectasis (Case XI), asbestosis [3] or trauma [21]. In addition to occurrence in the lung, localized aspergillosis may be present elsewhere, as in the feet [1], bowel mucosa [22], spinal cord [23] and pleural cavity [21,24].

Two varieties of localized secondary aspergillosis are recognized; one is a saprophytic process such as a mycetoma or focal growth (Cases II, VIII and possibly XI), and the other a chronic low grade infection, abscess or granulomatous process (Cases III, VI and X). Both types of infection may have serious implications if critically located. Hemoptysis may be found with either mycetomas or solid lesions, and occasionally may be massive [25] and affected by position [26]. Patients with mycetomas may have a chronic cough; Hemphill [27] describes a patient with severe paroxysmal cough apparently precipitated by the fungal mass acting as a ball-valve over a bronchial communication. Mycetomas may be entirely free within the surrounding cavity (Case VIII); this may be established radiologically by roentgenograms taken with the body in various positions.

Secondary aspergillosis may also be invasive in nature (Cases I, IV, V and VII). This type usually presents as a pneumonic process (and may be superimposed on a bacterial pneumonitis) and may lead to multiple abscesses (Case VII). Tissues other than the lung also may be invaded.

The final category of secondary aspergillosis is the generalized or disseminated variety which can be further subdivided into types associated with endocarditis and disseminated infection in the absence of endocarditis.

There are three cases of endocarditis due to aspergillus reported in the literature [28–30]. None of the three patients had pre-existing valvular damage; the lesions produced by the aspergilli were quite destructive and involved both sides of the heart. The case cited by Welsh and Buchness [28] was extraordinary in that three different species of aspergillus were recovered from different lesions.

Disseminated secondary aspergillosis unassociated with endocarditis has been reported by a number of authors [31–39]. In these cases the following tissues of the body were involved in at least one of the patients: lung, pleura, mediastinum, brain, meninges, spleen, liver, kidney, heart, pericardium, aorta, smaller vessels, thyroid, duodenum, bones, lymph nodes and

skin. In our Case IX the uterus also was involved. Generalized aspergillosis results from hematogenous and possibly lymphogenous spread. It is surprising that dissemination is not more common since the organism characteristically invades blood vessels producing vascular necrosis. Histologically the lesions are either abscesses or granulomas. The symptoms and signs depend primarily on the size and site of lesions.

Predisposing Factors. Primary aspergillosis occurs following occupational or other exposure to the fungus [*1–3*]. Aspergillosis is encountered in bird fanciers (it is an important disease in many species of birds), hair sorters, millers, threshers and others who inhale dust or grain particles, and in farmers and other workers who are constantly exposed to any form of dry or powdered vegetable matter. Aspergillus spores may be present in farm homes, stables and barns. Frequent reference has been made to the high incidence of chronic, progressive disease in the pigeon crammers (mouth-to-mouth feeding) of Paris and in hair sorters who are exposed through the use of contaminated rye flour in removing grease from hair. Other areas such as the external ear, the spinal cord and the vagina may be sites of primary infection.

Predisposing factors are of paramount importance in secondary aspergillosis. In addition to a suitable portal of entry, usually the lung or upper respiratory passages, a local lesion is commonly found in the form of an area of inflammation, abscess or bronchiectatic cavity. The vagina and infected uterus were the likely portal of entry in our Case IX. Zimmerman [*38*] has documented hematogenous spread to the lung from secondary invasion of a gastric ulcer. Of increasing importance is the presence of an underlying debilitating illness and iatrogenic factors conducive to fungus infection.

Table II is a summary of the twelve cases herein reported, with emphasis on predisposing factors. Seven of the eleven patients with secondary aspergillosis had carcinoma, leukemia or Hodgkin's disease. Seven patients also had either bacterial pneumonia or pneumonitis of undetermined etiology as an underlying lung disease. Three patients with secondary aspergillosis had had recent surgery, three had chronic pulmonary disease, two had chronic congestive heart failure, and two had serious infections other than pneumonia. Three of the eleven patients had marked leukopenia, two with granulocytopenia. Six of these eleven patients with secondary aspergillosis had received adrenocortical steroids (usually for long periods) and one had also received corticotropin.

The association of mycotic infections with the use of antibiotics and adrenal cortical hormones is well discussed by Torack [*40*] and Zimmerman [*28,38*]. Although we believe that steroids definitely predispose the host to secondary infection, we were unable to demonstrate a relationship between the dose and duration of steroid administration and the severity of secondary aspergillosis. However, Mankowski [*41*] has shown that cortisone-treated mice had a much more rapid death than control animals in experimental aspergillosis. This author also refers to an interesting report by Devillers and Revon which mentioned a woman with chronic membranous aspergillus bronchitis who experienced distinct flareups of her disease a few days prior to each menstruation; this suggests that other hormones also may be important.

Four patients received other "anti-neoplastic" therapy; included was radiation to the spleen, administration of Myleran,® Leukeran® and amethopterin. The possibility that antimetabolites may enhance other types of infections has been discussed by other authors [*42,43*]. Ten of our patients had received extended courses of multiple antibiotics; the other patient with secondary aspergillosis received small amounts of two antibiotics.

Table III summarizes twenty-four cases of aspergillosis from the literature in which the use of antibiotics and/or steroid hormones may have played a role. All patients had received antibiotics and/or sulfonamides. Seven of these twenty-four patients received adrenocortical steroids and/or corticotropin, two received radiation, one nitrogen mustard, and one urethane. As in our series, the presence of malignant or other debilitating diseases or injuries, leukopenia or granulocytopenia, pneumonitis, other infections and underlying pulmonary disease was noted frequently. Zimmerman [*38*] discusses these predisposing conditions and stresses the importance of local lesions as a portal of entry. Other possible factors predisposing to aspergillosis are splenectomy [*30,47*] (one in our series), prematurity [*35*], infancy [*31,38*], old age (our series) and possibly diabetes.

Pathology. In the lung, aspergillosis is most frequently associated with necrosis (probably attributable to both vascular obstruction and

toxin production by the organism), accompanied by acute or chronic inflammatory cellular infiltration [*48*]. Other changes include small granulomatous masses with Langhans-type giant cells (Fig. 1), areas of gray hepatization surrounded by a zone of emphysema, and cavity

TABLE II

SUMMARY OF CASES OF ASPERGILLOSIS BEING REPORTED

Case No.	Age (yr.), Sex	Underlying Disease(s)	Leukopenia?	Steroids (daily dose and duration)	Anti-Neoplastic Therapy	Antibiotics (daily dose and duration)	Type of Aspergillosis
I.	74, M	Squamous carcinoma, anus; recent abdominoperineal resection; bronchopneumonia	No	None	None	Sulfasuxidine, 8 gm. for 12 days; oxytetracycline, 1 gm. for 4 days; penicillin, 600,000 units for 6 days; streptomycin 1 gm. for 6 days; sulfisoxazole, 4 gm. for 9 days	Multiple pulmonary abscesses both upper lobes; up to 1 cm. in diameter; **invasive secondary aspergillosis**
II	62, M	Epidermoid carcinoma, lung; pancytopenia, etiology undetermined; hemolytic anemia; pneumonia, staphylococcic	900–1,800 white cells/cu. mm. 75–87% lymphocytes	Cortisone, 300 mg. for 9 days	None	Penicillin, 1.2 million units/day for 2 days; tetracycline, 1 gm. for 6 days	Necrotizing bronchitis, with superimposed aspergillus infection; **localized secondary aspergillosis**
III	30, M	Acute myelogenous leukemia; pyelonephritis; recent laminectomy; pneumonitis	No	Cortisone, 300 mg. for 23 days; 200 mg. for 8 days; 150 mg. for 17 days	Amethopterin	Penicillin, 3,000,000 units for 5 days; 1,200,000 units for 28 days; streptomycin, 1 gm. for 5 days; sulfisuxazole 4 gm. for 23 days; nitrofurantoin 400 mg. for 38 days; tetracycline, 300 mg. intramuscularly for 30 days; 2 gm. orally for 11 days	Two small granulomatous pulmonary nodules; **localized secondary aspergillosis**
IV	78, M	Fracture, right hip; surgical reduction of fracture; volvulus; bowel resection; surgical parotitis; staphylococcal bacteremia; aspiration pneumonia; chronic congestive heart failure	No	Hydrocortisone, 50–100 mg. for 19 days; ACTH, 15–20 mg. for 19 days	None	Penicillin, 10,000,000 units for 22 days; streptomycin, 2 gm. for 28 days; tetracycline, 1 gm. for 11 days; erythromycin, 1 gm. for 11 days; chloromycetin, 1 gm. for 2 days; bacitracin, 80,000 units for 6 days; sulfisoxazole, 2 gm. for 6 days	1.5 cm. cavity upper lobe of right lung; contains fungus ball; blood vessel invasion; **invasive secondary aspergillosis**

TABLE II (*Continued*)

SUMMARY OF CASES OF ASPERGILLOSIS BEING REPORTED

Case No.	Age (yr.), Sex	Underlying Disease(s)	Leukopenia?	Steroids (daily dose and duration)	Anti-Neoplastic Therapy	Antibiotics (daily dose and duration)	Type of Aspergillosis
V	35, M	Chronic myelogenous leukemia; Pneumonitis	Yes—2 mo. before death (following radiation); white blood cells decreased to 500 and then ran between 1,400 and 2,800 for 1 mo. before returning to normal and higher ranges (approximately 15% neutrophils during period of leukopenia)	Cortisone 75–225 mg. for 11 days	Radiation to spleen; Myleran	Tetracycline, 2 gm. for 45 days; erythromycin, 800 mg. for 11 days; 400 mg. for 4 days	Necrotizing pneumonitis; **invasive secondary aspergillosis**
VI	58, M	Bronchiolar carcinoma with widespread metastases; multiple old pulmonary infarcts (embolic); emphysema, bronchiectasis; cor pulmonale	No	None	None	Penicillin, 600,000 units for 14 days; 900,000 units for 28 days; streptomycin, 0.5 gm. for 16 days	Somewhat loculated 7.0 cm. abscess cavity in upper lobe of left lung at margin of carcinoma; **localized secondary aspergillosis**
VII	58, M	Hodgkin's disease	725–4,000 white cells/cu. mm. 80–90% polymorphonuclear leukocytes	Prednisolone 30–60 mg. for 78 days	Leukeran	Tetracycline, 2 gm. for 28 days; erythromycin, 1.5 gm. for 13 days; nystatin, 1,500,000 units for 13 days	Pneumonitis and numerous small pulmonary cavities with mycelium and fructification characteristic of A. fumigatus on culture; **invasive, secondary aspergillosis**
VIII	68, M	Bacterial pneumonia and lung abscess; congestive failure (hypertensive cardiovascular disease); emphysema	No	None	None	Penicillin, 1,000,000 units for 65 days; 5,000,000 units for 9 days; tetracycline, 1 gm. for 3 days; chloromycetin, 2 gm. for 117 days; erythromycin, 2 gm. for 62 days; streptomycin, 2 gm. for 2 days; sulfisoxazole, 4 gm. for 13 days; nystatin, 1,000,000 units for 11 days	Mycetoma; A. fumigatus found twice on culture; **localized secondary aspergillosis**

TABLE II (*Continued*)
SUMMARY OF CASES OF ASPERGILLOSIS BEING REPORTED

Case No.	Age (yr.), Sex	Underlying Disease(s)	Leukopenia?	Steroids (daily dose and duration)	Anti-Neoplastic Therapy	Antibiotics (daily dose and duration)	Type of Aspergillosis
IX	33, F	Septic abortion; shock, acute renal failure	No	None	None	Penicillin, 3.6–12.5 million units for 26 days; chloromycetin, 0.5–1.0 gm. for 21 days; erythromycin, 1.5 gm. for 5 days	Widely disseminated with involvement of uterus, heart, lungs, spleen, and brain; A. fumigatus on culture; **disseminated secondary aspergillosis**
X	47, M	Chronic lymphatic leukemia; pneumonitis, etiology undetermined	No	None	Leukeran	Penicillin, streptomycin and erythromycin for 1 mo. prior to admission; chloromycetin, 2 gm. for 24 days; novobiocin, 1 gm. for 10 days; sulfisoxazole, 4 gm. for 6 days; penicillin, 2–3 million units for 4 days; neomycin, 1 gm. for 8 days; polymyxin 90 mg. for 7 days; streptomycin, 2 gm. for 5 days; bacitracin, 80,000 units for 5 days; nystatin, 1,000,000 units for 10 days; amphotericin, 25 mg. for 3 days	Small abscesses and granulomas, upper lobe of left lung containing mycelium consistent with aspergillus A. fumigatus previously grown out of sputum 3 times; **localized secondary aspergillosis**
XI	39, M	Chronic pulmonary disease with bronchiectasis and pulmonary fibrosis; cor pulmonale	No	Prednisolone 15–20 mg. for 57 days	None	Oxytetracycline, 2 gm. for 36 days; penicillin, 1,200,000 units for 38 days; streptomycin, 1 gm. for 7 days; amphotericin, 25–50 mg. for 6 days	Localized bronchial infection?, A. fumigatus found on sputum culture two times; **localized secondary aspergillosis**
XII	67, M	None	No	None	None	None prior to onset, (nitrofurantoin subsequently)	Chronic granulomatous pulmonary involvement (bilateral); **invasive primary aspergillosis**

formation. Atherosclerosis in the pulmonary artery is common [*31*]. The fungi, if present, are single wide hyphae or matted masses of branching hyphae, and are usually easily discerned with routine hematoxylin and eosin stains. Kade and Kaplan [*49*] found that aspergilli

TABLE III

SUMMATION OF CASES OF ASPERGILLOSIS FROM LITERATURE IN WHICH ANTIBIOTICS AND/OR STEROIDS MAY HAVE PLAYED A ROLE

Author (Ref.)	Location and Type of Aspergillosis	Associated Fungal Disease	Underlying Disease(s)	Antibacterial Chemotherapy	Steroids	Other Antineoplastic Therapy
Torack [*40*]	Small granulomas of lung; **localized secondary aspergillosis**	Monilial ulceration of epiglottis, pharynx and esophagus	Carcinoma of breast; leukopenia	Nystatin for 36 days; penicillin for 24 days; streptomycin for 39 days; tetracycline for 71 days; erythromycin for 31 days	Cortisone for 65 days	Radiation therapy
Torack [*40*]	Necrotic focus in lung; **localized (?) secondary aspergillosis**	Monilial gastritis	Hodgkin's disease; pancytopenia	Penicillin for 23 days; streptomycin for 23 days	ACTH for 75 days; prednisone for 22 days; hydrocortisone for 76 days	None
Torack [*40*]	Abscess of lung; **localized secondary aspergillosis**	Monilial gastric ulceration	Carcinoma, bladder	Penicillin for 50 days; streptomycin for 50 days; erythromycin for 7 days; neomycin for 5 days; chloromycetin for 45 days; sulfisoxazole for 5 days	None	None
Welsh and Buchness [*29*]	Endocarditis and myocarditis; pulmonary abscesses; **disseminated secondary aspergillosis**	None	"Primary splenic neutropenia"; chronic interstitial pneumonitis; salmonella infection	Penicillin for 1 week; oxytetracycline for 2 weeks	ACTH and cortisone for 3 months	None
Welsh and McClinton [*36*]	Numerous small peribronchial abscesses; duodenal ulcer with extensive aspergillus invasion; **disseminated aspergillosis, either primary or secondary**	None	Swollen hemorrhoids; perianal slough (Aboard ship carrying grain)	Sulfadiazine for 9 days; penicillin for 12 days; oxytetracycline for 9 days	None	None
Cooper [*44*]	Numerous peribronchial abscesses; **invasive secondary aspergillosis**	None	Ruptured duodenal ulcer; peritonitis (2 operations)	Sulfadiazine	None	None
Grekin et al. [*33*]	Disseminated—brain, myocardium, lungs, thyroid, duodenum, and kidneys; **disseminated aspergillosis, either primary or secondary**	None	Respiratory infection (?)	Penicillin; sulfadiazine; chlortetracycline; streptomycin	None	None

TABLE III (*Continued*)

SUMMATION OF CASES OF ASPERGILLOSIS FROM LITERATURE IN WHICH ANTIBIOTICS AND/OR STEROIDS MAY HAVE PLAYED A ROLE

Author (Ref.)	Location and Type of Aspergillosis	Associated Fungal Disease	Underlying Disease(s)	Antibacterial Chemotherapy	Steroids	Other Antineoplastic Therapy
Wybel [23]	2.5 granuloma surrounding and distorting spinal cord; quadriplegia; **localized secondary aspergillosis (fatal by virtue of location)**	None(?)	Pneumococcal meningitis	Sulfadiazine; penicillin intramuscularly for 16 days; penicillin, intrathecally for 12 days	None	None
Darke et al. [30]	Extensive bilateral pneumonia with scattered abscesses; involvement of spleen; **disseminated secondary aspergillosis**	None	Pneumonia	Sulfonamides; tetracycline; chloromycetin	None	None
Zimmerman [28]	Endocarditis, ruptured intraventricular septum; **disseminated secondary aspergillosis**	None	Multiple injuries	Penicillin for 7 weeks (?)	None	None
Zimmerman [38]	Disseminated—lung, pleura, pericardium, brain, liver; **disseminated secondary aspergillosis**	None	(Newborn) Staphylococcal pneumonia	Penicillin; streptomycin	DOCA; cortisone 1 mo. (?)	None
Zimmerman [38]	Lung abscess; **localized secondary aspergillosis**	None(?)	Hodgkin's disease; pancytopenia	Yes—not specified	None	X-ray; nitrogen mustard
Zimmerman [38]	Invasion of gastric ulcer and metastatic lung abscesses; **disseminated secondary aspergillosis**	None(?)	Chronic lymphatic leukemia	Penicillin	ACTH; cortisone	None
Abbott et al. [45]	Extensive bronchopneumonia, 2 lobes with one 5 cm. cavity; **invasive secondary aspergillosis**	None	Postinfluenzal bronchopneumonia	Penicillin for 5 days; chloromycetin for 11 days; streptomycin for 5 days	None	None
Cawley [31]	Chronic pulmonary, later disseminated—brain, heart, lungs, spleen, liver, kidneys, ankle, dura, nodes; **disseminated secondary aspergillosis**	None	(Newborn) Pneumonitis(?)	Sulfonamides; penicillin	None	None

TABLE III (*Continued*)

SUMMATION OF CASES OF ASPERGILLOSIS FROM LITERATURE IN WHICH ANTIBIOTICS AND/OR STEROIDS MAY HAVE PLAYED A ROLE

Author (Ref.)	Location and Type of Aspergillosis	Associated Fungal Disease	Underlying Disease(s)	Antibacterial Chemotherapy	Steroids	Other Antineoplastic Therapy
Rankin [*31*]	Disseminated—lung (thrombi→infarcts), liver, spleen, kidney; **disseminated secondary aspergillosis**	Generalized moniliasis, chiefly in gastrointestinal tract	Agranulocytosis (chloromycetin)	Sulfonamides; penicillin; chloromycetin	None	None
Kirschstein and Sidransky [*30*]	Endocarditis tricuspid valve, myocarditis, pulmonary granulomas with necrosis, involvement of many pulmonary arteries and veins; **disseminated secondary aspergillosis**	None	Pancytopenia; chronic lymphatic leukemia(?); splenectomy	Tetracycline and oxytetracycline for 2 mo; penicillin for 16 days; streptomycin for 16 days	ACTH 20–30 units for 2 mo.	None
Levy and Cohen [*37*]	Generalized abscesses brain, heart, lung; **disseminated secondary aspergillosis**	Generalized moniliasis, lung, lymph nodes, spleen	Anemia and thrombocytopenia, etiology(?); staphylococcal sepsis	Penicillin for 14 days; sulfadiazine for 5 days	ACTH 25 units to 100 units for 4 months	None
Tobler and Minder [*35*]	Generalized—abscesses in lungs, lymph nodes, cerebellum, vertebrae, rib; **disseminated secondary aspergillosis**	None	Prematurity; ascariasis; hemolytic anemia	Chlortetracycline, 7.7 gm.; chloromycetin, 32 gm.	None	Urethane
Yesner and Hurwitz [*46*]	Pulmonary cavity, solitary; **localized aspergillosis, either primary or secondary**	None	Lung abscess(?)	Sulfonamide	None	None
Kligman [*22*]	Local infection in bowel mucosa (two patients)—not clinically manifest; **localized secondary aspergillosis**	None	Severe, chronic diarrhea, etiology(?)	Sulfasuxidine; oral streptomycin	None	None
Friedman et al. [*18*]	Localized pulmonary mycetoma; **localized secondary aspergillosis**	None	Pulmonary tuberculosis	Streptomycin; and PAS for 8 months	None	None
Golebiowski [*21*]	Empyema; **localized secondary aspergillosis**	None	Pulmonary tuberculosis; recent gastrectomy; segmental pulmonary resection	Streptomycin for 11 months; INH for 14 months	None	None

stained well also with Giemsa and Schiff reagent stains, of which the Gridley stain was best.

Occasionally, a cavity may contain a branching matted mass of hyphae, the so-called "fungus ball" or mycetoma. A fibrotic capsule is associated with this cavity formation and only rarely are fungi noted in the wall or in the surrounding tissue. It is uncertain whether bronchial dilatation or bronchiectasis precedes or follows the fungus infection; it is probable that both occur. In the report by Pesle and Monod [*26*] two patients did show bronchiectasis in other areas of the lung not involved by aspergillus. In the non-cavitary necrotic type of pulmonary disease, the fungi invade the surrounding alveolar walls and show some predilection for the walls of blood vessels, at times causing thrombosis.

On occasion (Case VII) one may see conidiophores in preparations of pulmonary aspergillosis, usually in association with cavities. (Fig. 3.) It should be emphasized that, strictly speaking, a tissue diagnosis of aspergillosis is justified only if recognizable conidiophores are seen. The hyphal elements are difficult to distinguish from those of penicillium, candida or mucor, but typically the mycelium of mucor is non-septated and exhibits marked irregularity of width, and candida tends to have considerably smaller septate hyphae with less lateral branching and more uniform staining; with candida, furthermore, small rounded spore forms are usually present in large numbers. However, it is possible to confuse hyphae cut in cross-section with spores. Penicillium and aspergillus cannot be distinguished in tissues in the absence of typical conidiophores and spores; penicillium, however, rarely causes deep-seated infection. Cryptococcus can be eliminated from practical consideration if true mycelial structures are demonstrable in tissues [*28*]. Occasionally in aspergillosis one sees "actinomycetoid bodies" resembling the sulfur granules of actinomycosis or nocardiosis [*6*]; however, the filaments are much larger than those of actinomyces or nocardia.

In disseminated aspergillosis the histopathologic appearance is similar to that described in the lung except that cavity formation is seldom encountered; abscess formation is characteristic. Dissemination is primarily hematogenous and in metastatic sites the fungi are most often noted growing through the walls of small vessels into the surrounding tissue.

Diagnosis. Pulmonary aspergillosis is usually diagnosed at autopsy, although if the disease is suspected it may be tentatively diagnosed with relative ease during life by mycologic examination of the sputum or bronchial lavage specimen. Direct microscopic examination of sputum may reveal fragments of septate hyphae that are often branched. Identification usually depends on culture.

Aspergillus species grow rapidly on a wide variety of simple media. Media containing penicillin and streptomycin or chloramphenicol are satisfactory, but cycloheximide (Actidione®) must not be used. Speciation in the genus aspergillus is a complex problem requiring considerable mycologic experience. A. fumigatus is the most common pathogen but the following species have been implicated in human disease: A. niger, A. versicolor, A. clavatus, A. nidulans, A. flavus, A. oryzae, A. glaucus and A. sydowi. Henrici [*48*] isolated an endotoxin from A. fumigatus which is pathogenic for rabbits receiving intravenous injection.

Aspergilli are not only common laboratory contaminants but also, because of their ubiquitous nature, may be found in a wide variety of clinical specimens. In the absence of histologic material care is required in making a diagnosis of aspergillosis. The presence of the fungus may represent the overgrowing of a more obscure but primary infectious agent or a contaminant introduced in the specimen collection or laboratory. The *repeated* isolation of aspergillus from clinical material in the absence of a more obvious pathogen is good evidence of aspergillosis but is still inconclusive. Recovery of the organism from unexposed sources (such as empyema fluid) or from tissues helps provide definitive diagnosis.

Cases VII, VIII, IX, X and XII can be considered as diagnosed unequivocally because of morphologically typical fungi noted in biopsy, operative or autopsy specimens, together with recovery of aspergillus on culture on one or more occasions from each patient. In Case XI the diagnosis must be considered questionable; although the fungus was recovered twice on culture of the sputum there was no clinical evidence of aspergillosis outside the bronchial tree and we were unable to find fungi in a review of lung tissue obtained elsewhere. Cases I, II, III, IV, V and VI are clinically and pathologically suggestive of aspergillus infection, and fungi consistent with (but not diagnostic of) aspergillus were seen in the tissue sections; unfortunately, no cultures were made in these cases.

The protean manifestations of the disease make it difficult to diagnose. However, primary aspergillosis localized to the bronchial tree is easily recognized by the finding of the fungus in the expectorated mucous plugs [3]. The primary forms should be looked for in patients exposed to grains, dry vegetable matter or birds. Aspergillosis should be considered in the differential diagnosis of granulomatous diseases and it should be thought of especially (along with other fungus diseases) in patients with debilitating illnesses who have received antibiotics or adrenocortical steroids.

Skin tests and serologic studies give inconsistent results and are not useful diagnostically. X-ray findings are variable and not diagnostic. Infiltration into the lungs is usually basal in location. A suggestive x-ray feature is an increase of the hilar shadows with radiating spider-web appearance—the "sun-burst" effect [50]; this finding may be seen in various fungus diseases as well as in other conditions. The x-ray picture of pulmonary mycetoma is quite unique. The literature on mycetomas has been reviewed by Levin [51] and by Lodin [52] who point out that mycetomas can be caused by candida or streptomyces occasionally. However, most pulmonary mycetomas are due to aspergillus and the typical x-ray picture warrants a tentative diagnosis of aspergillosis. The typical mycetoma as seen on roentgenograms is a mass with a thin, crescentic aerated area at the upper pole; the cavity is enclosed by a thin line, as in an air cyst. (Fig. 5.)

Treatment. Drug therapy for aspergillosis has not been generally effective. Iodides have been recommended for a number of years but it is clear that the results have often been disappointing. Desensitization is recommended for the allergic type of migrating pneumonitis by Smith [53]. Although transitory improvement has been reported with the intravenous administration of hydroxystilbamidine [54], others have reported treatment failure [55,56]. Riddell [57] found that inhalations of nystatin in suspension, solutions of brilliant green or hydroxystilbamidine were effective in suppressing or removing A. fumigatus from the bronchial secretions.

Nystatin will probably not be useful except in unusual cases in which it might be used topically. Parenterally administered amphotericin [58] and pimaricin have not had an adequate trial and probably offer the best possibilities for treatment at present. Eulicin [59] is very active *in vitro*, but toxicity may limit its usefulness. Cycloheximide (Actidione) is no longer available for parenteral use. Griseofulvin showed no promise in the one patient we treated (Case XII).

Although currently available medical therapy for aspergillosis leaves much to be desired, it is likely that more favorable results would be obtained if patients were diagnosed and treated earlier. Prophylaxis in the form of rational use of antibiotics and adrenocortical steroids is an important consideration.

Surgical therapy is indicated for drainage of abscesses and excision of localized lesions. Apparently the first successful surgery for a pulmonary mycetoma in the United States was reported by Gerstl, Weidman and Newmann [32] in 1948. Many others have since been noted in the literature. Surgical treatment has been used in solid pulmonary lesions [25], empyema [21,24] and abscess of the brain [16,60].

Prognosis. The prognosis in primary aspergillosis is poor in cases of the invasive or generalized variety, but is usually good in localized disease. The prognosis in secondary aspergillosis is further modified by the nature and extent of the underlying disease. All eleven patients with secondary aspergillosis in our series died; the aspergillosis was considered to be either the primary cause of death or a significant contributing factor in Cases I, V, VII and IX.

Associated Fungus Diseases. Table III lists five patients with aspergillosis and co-existing candida infections (all invasive); our Case II was similar, and in our Case V the patient may have had an associated Candida ulceration.

SUMMARY AND CONCLUSIONS

The clinical and pathologic data in twelve cases of aspergillosis are presented. Eleven patients came to autopsy; one is still living. One of the patients had primary aspergillosis; the others all had secondary involvement. The eleven patients with secondary aspergillosis all had debilitating underlying diseases and had received antibiotic therapy, usually multiple drugs, for a prolonged period. Six of these patients had received adrenocortical steroids or corticotropin. Three were leukopenic. Similar cases of aspergillosis from the literature in which the use of antibiotics and/or steroids may have played a role are tabulated. Possible predisposing causes other than these are listed.

A new classification of aspergillosis is presented.

The diagnosis of aspergillosis is difficult.

Early diagnosis would probably improve results of medical treatment. Surgery is effective in drainage of abscesses and resection of localized lesions. Prophylaxis through more judicious use of antibiotics and steroid hormones is most important even though the use of antibiotics and steroid hormones may be unavoidable; in these situations one should be alert to the possibility of superimposed aspergillus (as well as other fungal and bacterial) infection.

Acknowledgment: We wish to thank Dr. W. S. Adams, Professor of Medicine, University of California School of Medicine, Los Angeles, for permission to include Cases VII and X; Dr. J. D. Kirshbaum, San Bernardino County Hospital, for the autopsy specimens in Case XI; and Drs. Dexter Howard and Orda Plunkett of the University of California, Los Angeles for assistance in identification of some of the aspergilli.

ADDENDUM

Since the manuscript was completed we have encountered another case of disseminated aspergillosis, in this instance associated with other mycoses. A twenty-eight year old student entered Wadsworth General Hospital in 1959 for treatment of lymphosarcoma established six months previously. The past history included a diagnosis of coccidioidomycosis in 1956 (confirmed by a complement fixation test) that apparently healed without incident. Treatment for his lymphoma consisted of high doses of prednisolone, prolonged use of a wide variety of antibiotics, radiation, nitrogen mustard, chlorambucil, 5-fluorouracil and 6-mercaptopurine. A persistent infiltration was seen on his chest roentgenogram. Oral ulcerations repeatedly yielded cultures of Candida albicans, and sputum cultures grew aspergillus twice and Coccidioides immitis once. Two blood cultures revealed aspergillus and one of them in addition grew C. immitis. These disseminated mycoses were the immediate cause of death. Autopsy findings and further laboratory studies will be reported when more complete data are available.

Two additional cases of secondary aspergillosis in the form of large pulmonary abscess cavities have recently been reported [*61*]; iodide therapy cleared the sputum of aspergillus but also produced toxic manifestations.

An additional experimental study has recently been published by Sidransky and Friedman [*62*]; this study demonstrates increased susceptibility to aspergillosis in mice treated with cortisone or with cortisone plus antibiotics.

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Clinicopathologic Conference

"Adult" Mucoviscidosis

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine, and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was a seventeen year old girl who was admitted to the Barnes Hospital for the second time on March 22. She died on March 29, 1959.

The patient was first seen at St. Louis Children's Hospital in 1942 when she was several months of age. She was admitted for evaluation of abdominal pain and hematuria and was found to have an infection of the urinary tract. She received treatment for this and for moderately severe dehydration with prompt relief. The patient was discharged after ten days of hospitalization. Twelve days after discharge she was rehospitalized at St. Louis Children's Hospital because of moderately severe emesis. The vomiting was of brief duration and was unattended by diarrhea or any other manifestations of gastrointestinal dysfunction. Physical examination on this admission revealed an acutely and somewhat chronically ill infant, with a protuberant abdomen. She received no specific therapy and was discharged three days later. There was no evidence of recurrence of the infection of the urinary tract.

The patient's last admission to the St. Louis Children's Hospital was in 1946 when she was four years old. On this admission, a history was obtained of frequent large, bulky, foul smelling, and greasy stools, beginning at age nineteen months. Such stools were noted on the average of every two weeks, but their frequency had been noted to have increased during the months just before the patient was hospitalized in 1946. Her appetite had always been excellent but despite this she had failed to gain weight. Pastries and foods high in starch content, had been particularly liable to precipitate the diarrhea. The patient had had repeated respiratory infections throughout this time, with cough and production of moderate amounts of sputum. A sister had died at the age of five months with a clinical diagnosis of interstitial bronchopneumonia; however, no autopsy was performed.

The physical examination revealed an underdeveloped, undernourished, pale child with a protuberant abdomen. There were no abdominal masses or organs palpated. Pertinent laboratory data during this admission included the presence of many Sudan III stained fat droplets in the stool, and a glucose tolerance test revealing a fasting blood sugar (capillary blood) of 72 mg. per cent, thirty-minute specimen 132 mg. per cent, sixty-minute specimen, 139 mg. per cent, two-hour specimen 112 mg. per cent, and three-hour specimen 81.5 mg. per cent. Roentgenograms of the chest were interpreted as showing bronchial thickening of undeterminant nature. The possibility of tuberculosis was suggested but the first strength PPD was negative. An assay of fluid obtained by duodenal drainage revealed complete absence of tryptic activity. The child was then begun on a therapeutic regimen including a high calorie, high protein, low starch and low fat diet, vitamins, pancreatic granules and prostigmine bromide. She was subsequently discharged to be followed up by her physician.

During the succeeding twelve years, the patient was followed up by her private physician and was not rehospitalized at St. Louis Children's Hospital. Throughout this time, she continued to have recurrent respiratory infections associated with cough, productive of mucoid and mucopurulent sputum frequently without fever. She received antibiotic therapy repeatedly. Slight exertional dyspnea became apparent but this was minimal. She was never noted to be cyanotic. Swelling of the ankles occurred on one occasion, but she never had abdominal swelling.

During this twelve-year period the patient

had infrequent intermittent episodes of loose, foul, bulky stools. Her weight at age sixteen was 70 pounds, despite a good appetite.

Two weeks before admission a respiratory infection developed associated with productive cough, fever and shortness of breath. Because of the persistence of these symptoms she was admitted to the Barnes Hospital for the first time on September 29, 1958.

Physical examination revealed a small, thin, chronically ill female, in no acute distress. The vital signs were within normal limits. Significant findings were moderate pallor, and marked clubbing of the fingernails and toenails. There was a moderate increase in the anteroposterior diameter of the chest, and wheezes, rhonchi, and many fine and coarse rales were heard. Examination of the heart was not unusual except for a soft precordial murmur throughout systole and an accentuated pulmonic second sound.

On admission, laboratory data revealed a hematocrit of 22 per cent; white blood cell count, 17,000/cu. mm.; differential count: eosinophils, 1 per cent; segmented forms, 81 per cent; lymphocytes, 16 per cent; and monocytes, 2 per cent. There was moderate hypochromia of the erythrocytes. Urinalysis disclosed a specific gravity of 1.029; reaction, 4.5; negative for albumin and reducing substances. Rare red blood cells were noted on microscopic examination of the urine sediment. Stool examination revealed a trace reaction for occult blood. Results of the cardiolipin test were negative. Blood chemistries were: non-protein nitrogen, 17 mg. per cent; fasting blood sugar, 69 mg. per cent; cholesterol, 129 mg. per cent; total serum proteins, 5.8 gm. per cent; albumin, 3.3 gm. per cent; globulin, 2.5 gm. per cent; prothrombin level, 100 per cent of normal; sodium, 140 mEq./L.; potassium, 4.1 mEq./L.; chloride, 95 mEq./L.; and CO_2 combining power, 34.2 mEq./L. An electrocardiogram was interpreted as showing sinus tachycardia. Roentgenographic examination of the chest was interpreted as being consistent with pulmonary emphysema, with questionable fibrotic tuberculosis of the upper lobe of the left lung and extensive chronic pneumonitis suggestive of underlying bronchiectatic disease. Repeat stool examinations revealed persistent positive guaiac reactions.

The patient was hospitalized for six days. During this time she was noted to have daily temperature elevations but the temperature never exceeded 38.5°C. She continued to appear chronically ill, and during this time dyspnea became increasingly apparent. Therapeutic measures included the administration of antibiotics, bronchodilators, expectorants, fluids, vitamins, pancreatic granules, and postural drainage. She improved on this regimen and was discharged on October 4, 1958.

The patient was admitted to the Barnes Hospital for the second time on March 22, 1959. During the interval the patient had noted increasingly frequent diarrheal stools, and she had lost approximately 7 pounds of weight. Five days before this admission, rhinorrhea, sore throat and cough developed. Following this, her temperature rose to 101°F., but there was no increase in dyspnea. On the day prior to admission, she took only fluids, and had one episode of hemoptysis.

Physical examination revealed a thin, pale, chronically and acutely ill girl who was lethargic, dyspneic, and cyanotic. Her blood pressure was 110/80 mm. Hg; pulse, 128/minute; respirations, 28/minute; temperature, 38.2°C. (oral). The skin was pale and dry. The cervical veins were distended in the sitting position. Auscultation of the chest revealed the presence of many fine moist and sticky rales throughout the lower two-thirds of both lung fields. The heart was not enlarged to percussion, the rhythm was regular, and there were no cardiac murmurs. A hepatic edge was palpated 5 cm. below the right costal margin. There was marked clubbing of the fingernails and toenails. The neurologic examination was within normal limits.

Laboratory data on admission were: hemoglobin, 14.3 gm. per cent; white blood cell count, 22,250/cu. mm.; differential: band forms, 11 per cent; segmented forms, 74 per cent; lymphocytes, 14 per cent; and monocytes, 1 per cent. Urinalysis demonstrated a specific gravity of 1.023; reaction, 4.5; negative for albumin and reducing substances; there were a few white blood cells per high power field in the sediment. A stool was well formed, light brown, with trace benzidine reaction and positive for neutral fat. Sedimentation rate (corrected) was 37 mm. per hour. Blood chemistries were: nonprotein nitrogen, 13 mg. per cent; cholesterol, 84 mg. per cent; sodium, 126 mEq./L.; potassium, 4.6 mEq./L. Results of the cephalin-cholesterol flocculation test were negative; thymol turbidity, 1.1 units; and total serum bilirubin, less than 0.8 mg. per cent. An electro-

cardiogram was interpreted as being consistent with right ventricular strain, counterclockwise rotation, sinus tachycardia, and right axis deviation. The circulation time was fourteen seconds (arm to tongue), and the venous pressure was 120 mm. of saline.

The patient was critically ill. She was treated with fluids, oxygen, antibiotics, and digitalis. During the first forty-eight hours she remained lethargic, cyanotic and dyspneic. Because of the hyponatremia she was given corticosteroids intravenously, and hypertonic saline. Following these measures she appeared to improve with lessening of the dyspnea; however, this improvement was brief and within the following forty-eight-hour period, once again severe dyspnea developed, and she became disorientated and intermittently agitated. Repeat serum electrolytes on the day of her death were sodium, 135 mEq./L.; potassium, 3.6 mEq./L.; chloride, 67 mEq./L.; and CO_2 combining capacity, 47.5 mEq./L. During the last day of the patient's life, she became increasingly tachypneic followed by short, rapid, and gasping respirations. She died quietly on the eighth hospital day, March 29, 1959.

CLINICAL DISCUSSION

DR. EDWARD H. REINHARD: Dr. Humphrey, would you like to discuss the roentgenograms?

DR. HARVEY A. HUMPHREY: The first and only examination of the chest showed pulmonary emphysema. The heart appeared small. There was considerable infiltration and fibrosis throughout the lungs bilaterally and symmetrically. The hilar regions were enlarged, with a combination of hilar adenopathy and dilated pulmonary arteries. The main pulmonary artery was dilated. There was good evidence of chronic bronchitis, chronic bronchopneumonia, and very marked emphysema. Calcification was present in the upper lobe and hilar nodes of the right lung. There was also evidence of a dilated bronchus which was suggestive of some bronchiectasis. The most likely diagnosis would be mucoviscidosis with pulmonary emphysema, chronic bronchopneumonia, hilar adenopathy, and evidence of pulmonary hypertension. Additional findings included some right ventricular enlargement, and examination of the paranasal sinuses revealed them to be airless.

DR. REINHARD: This patient was diagnosed at the Children's Hospital and at the Barnes Hospital (on both admissions) as having fibrocystic disease of the pancreas or mucoviscidosis. Dr. Shatz, I wonder if you would agree with this as the most likely diagnosis? Do you think there are any other gastrointestinal diseases which we have to consider in the differential diagnosis?

DR. BURTON SHATZ: The presence of symptoms in this patient since infancy characterized by diarrhea, bulky, foul smelling stools, which contained greasy material that gave a positive fat stain are all compatible with the malabsorption syndrome. There is no evidence of any primary small intestinal disease to explain this malabsorption, therefore, the absorptive disturbance must be secondary to pancreatic insufficiency. In a child this age, the concomitant findings of chronic pulmonary infection with malabsorption indicate a diagnosis of mucoviscidosis. The other gastrointestinal lesion which may occur in patients with mucoviscidosis is biliary cirrhosis. This would be particularly true in a patient who survived as long as seventeen years, and a liver which was palpable below the costal margin did develop in this patient.

DR. REINHARD: Dr. Klingberg, how often do you see the malabsorption syndrome unassociated with fibrocystic disease of the pancreas in infants and children?

DR. WILLIAM G. KLINGBERG: Fibrocystic disease is the most common cause of the celiac picture in the United States.* True celiac disease is less common, but it is seen in subjects with gluten intolerance and starch or fat intolerance.

DR. REINHARD: As far as the pulmonary lesion is concerned, the differential diagnosis lies between mucoviscidosis and bronchial asthma. In mucoviscidosis, the primary change in the lung is bronchial obstruction by thick mucus leading to generalized obstructive emphysema complicated by recurrent secondary infection. Dr. Noah, this is basically the same sequence of events that occurs in bronchial asthma, is it not?

DR. JOSEPH NOAH: That is correct, Dr. Reinhard, in that one finds this sort of obstruction of the bronchial tree in asthma primarily of the type called infective or intrinsic asthma. This is not the type commonly seen in children. The presence of thick bronchial secretions in an older asthmatic person is probably the primary therapeutic problem with which one has to

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contend. These children with mucoviscidosis apparently have the same type of secretion and similar problems.

DR. REINHARD: I would like to emphasize one thing you said. This patient did not have anything to suggest an allergic type of extrinsic asthma. How common is intrinsic asthma or infective asthma in children?

DR. NOAH: I think it is quite uncommon. I might add that occasionally allergic asthma does occur in a child with mucoviscidosis and in that instance one must look to the family history, the presence of the eosinophils in the sputum and to a personal history of allergy in order to establish the diagnosis.

DR. REINHARD: I was impressed upon reading about this that a fair number of children with mucoviscidosis actually do wheeze. This, of course, is the result of obstruction due to the mucus and does not imply that there is bronchial spasm on an allergic basis. How do you make the diagnosis of an allergic type of bronchial asthma in a patient who has mucoviscidosis?

DR. NOAH: I think one has to be very careful. Evidence must be obtained for various sensitivities based on, perhaps, the history of seasonal increase in symptoms associated with pollen, dust or something of the sort, or a history of sensitivity to ingestants, plus the laboratory finding of a large number of eosinophils in the sputum.

DR. REINHARD: From this point on we are going to assume that the diagnosis of mucoviscidosis was established and we will discuss the various facets of this fascinating disease. First let us consider the genetics of this disease. Dr. Klingberg, what is known about hereditary factors in fibrocystic disease of the pancreas? In discussing this I wonder if you would comment on the fact that this patient's sister died at five months of age of interstitial bronchopneumonia, but unfortunately no autopsy was performed. Do you think this child probably had mucoviscidosis?

DR. KLINGBERG: I think that is a very good possibility. Mucoviscidosis occurs in more than one sibling quite frequently. It is probable that this disease is inherited as a recessive trait. The major difficulty arises in demonstrating the recessive character in both the mother and father; to date this has not been very satisfactory. It certainly seems to be true that the mother or father, or both, may have symptoms of emphysema or minor gastrointestinal complaints more commonly than in the normal population. On the other hand, other tests are relatively normal with the exception that some of them have been demonstrated to have abnormal sweat chloride tests.

DR. REINHARD: This occurrence of abnormal reactions to sweat chloride tests in parents suggests that there is a form fruste, right?

DR. KLINGBERG: Yes, and this is the only type of supporting data we have. If both parents show the recessive genes then at least 25 per cent of the children will be involved, although in some families higher percentages than this will be found.

DR. REINHARD: I would like to discuss the embryologic development of the pancreas and lungs in relation to the pathogenesis of the lesions of this disease. In the fifth week of gestation the 5 mm. embryo shows the beginning of the development of the pancreas by two outgrowths from the endodermal lining of the gut. At about this same time the epithelial anlage of the respiratory system appears on an outgrowth of the pharyngoesophageal border. During the seventh week fusion of the two portions of the pancreas into a single organ occurs. The ventral pancreas forms the head, and its duct becomes the main outlet of the pancreas, that is the duct of Wirsung. The dorsal duct becomes the accessory duct of Santorini. At this time the epithelial lining of the duodenum, the esophagus, and the rectum grow more rapidly than does the intestinal tube itself and this results in temporary occlusion of the gastrointestinal tract in the esophagus, in the vicinity of the duodenum and in the rectum. A physiologic occlusion of the pancreatic duct does not occur at this or any other time. By the seventh week the celiac plexus has become recognizable in the paravertebral area. By the tenth week histologic differentiation of the pancreas has begun. There is beginning formation of acini which originate as terminal or lateral buds from the ducts. The islands of Langerhans are present at fourteen weeks. The islands of Langerhans, like the acini, are products of differentiation from the ducts. By the sixteenth week, meconium begins to appear in the gut. By this time also mucin cells are present in the salivary glands, and by the sixteenth week sweat glands are detectable as epithelial buds but lumens have not as yet developed. This does not occur until the seventh fetal month.

We might now go on to consider briefly the

development of enzyme activity in this system. Trypsin can be found in the duodenum in the fourth month, occasionally as early as the sixteenth week. Pancreatic amylase has been found as early as twenty-two weeks; pancreatic lipase does not appear until about thirty-two weeks. Sampson has studied the increasing quantity of trypsinogen in the developing fetal pig. About the sixth or seventh week there is a rapid development of tryptic activity which reaches almost adult activity by the tenth week. Now seven weeks of gestation represents the mid-point of pregnancy in the pig and this would therefore correspond to sixteen to eighteen weeks of gestation in man.

With this as background, Dr. Klingberg, would you discuss the problems of meconium ileus disease?

DR. KLINGBERG: Meconium ileus is one of the complicating features of fibrocystic disease of the pancreas as seen in the newborn baby. It is caused by the lack of secretion of trypsin which is a part of the pathology of cystic fibrosis. With absence of trypsin within the gut, the meconium becomes quite sticky and tenacious. There is lack of liquefaction, which is the primary action of trypsin on meconium, and because of this an obstructive picture may develop. The incidence of cystic fibrosis is roughly 1.73 per 1,000 live births. The incidence of meconium ileus disease is much more difficult to come by. The clinical picture in the newborn baby is typically that of a normal baby at birth, who within a matter of hours to one or two days, becomes obviously obstructed. The tremendous distention that occurs in these babies requires an emergency surgical procedure and it is not at all uncommon for the gut to rupture and meconium peritonitis ensue. One is always faced with the problem of locating the obstruction and the baby must have a barium enema. If the large bowel is normal and of very small diameter, it indicates that it has not been filled with meconium during fetal life and therefore this helps pinpoint the obstruction to the area of the ileum. One should not mistake this for meconium peritonitis of intrauterine life. In this latter disease flecks of calcium are to be found throughout. This sort of picture occurs when there is an intrauterine obstruction of the intestine with rupture. Meconium gets out into the peritoneal cavity and leads to calcification as you see. Occasionally a child survives meconium ileus disease only to have obvious signs of fibrocystic disease develop as time goes on.

DR. REINHARD: Dr. Klingberg, I wonder if you would discuss current concepts regarding the basic lesions in mucoviscidosis, keeping in mind that any satisfactory explanation must explain lesions in the lungs, the liver, and perhaps other organs as well as the pancreatic lesions? Has anyone been able to produce this disease experimentally?

DR. KLINGBERG: Farber, in Boston, injected large doses of parasympathomimetic drugs into newborn kittens for a long period of time. He was able to produce inspissation of mucus within mucous-forming glands throughout the body and has been able to stimulate the picture of pancreatic fibrosis to some degree. Some people believe that the lesion of mucoviscidosis resides within the pancreas itself, leading to the cystic dilatations, with the deficiency of pancreatic juices and poor absorption of vitamin A in particular, this latter deficiency resulting in the secondary more widespread changes of metaplasia of respiratory tract, and genitourinary tract epithelium. Others believe that this is a disease of the mucous gland in general. Certainly changes can be found in mucous glands throughout the body.

DR. REINHARD: As pointed out by Dr. Klingberg we do not have the answer to even the cellular locus of the lesions and therefore it is probably futile to try to go on and discuss the actual histochemical changes that occur in this disease. I think it would be wise to consider briefly the mucus which appears in the intestine and in the respiratory and biliary tracts in this disease. It is possible that the mucus itself may be abnormal when it is secreted, or perhaps that there is a failure to break down and depolymerize the normal mucus after it is secreted. Dr. Middelkamp, do you have any data about which of these two mechanisms is correct?

DR. J. NEAL MIDDELKAMP: At present I think no data is available to determine which of these two theories is correct. Dr. Dische, at the University of Chicago, has analyzed the mucus and specifically the mucoid fraction present in the duodenal juice in normal persons and in persons with fibrocystic disease. He has found these values to be of the same general range in both groups of patients when measured in mg./100 ml. of duodenal juice secreted. Dr. Landing at the University of Cincinnati has used another approach studying the nature of the mucus in these patients, namely by histochemical staining. He studied a number of the mucous-secreting

glands throughout the body including the stomach, small intestine, those present in the colon as well as the bronchial epithelium, pancreas and biliary tree. He, too, cannot arrive at any specific difference in the mucins present in normal persons as opposed to those present in persons with fibrocystic disease. The only slight evidence he had was that the mucin found in the patient with cystic fibrosis is slightly more resistant to digestion by trypsin than that found in normal persons.

DR. REINHARD: Dr. Sherry, do you have anything to add to this?

DR. SOL SHERRY: The major problem in the analysis of mucus related to the fact that mucus represents a complex of mucoproteins rather than a single substance. In studies by Odin and others reviewed in a recent Ciba Symposium, it was pointed out that there are at least three types of mucoproteins present in normal epithelial mucus; two groups of glycoproteins and a group of sulfated mucopolysaccharides. The prevalent type of glycoprotein called fucomucins have L-fucose as the main carbohydrate, although hexosamines are also present. Then there are the sialomucins containing sialic acid as the main carbohydrate component and finally, in much smaller amount, the sulfated mucopolysaccharides. An analysis of the mucus in mucoviscidosis should consider each of these particular types of mucoprotein. I have been intrigued by the possibility that there may be a generalized enzymatic defect in mucoviscidosis. Proteolytic enzymes are secreted by various mucous glands which aid in the liquefaction of the mucus after it has been secreted; perhaps these enzymes are absent, not only in the pancreas, but also in the lung and other areas as well.

DR. REINHARD: Dr. Middelkamp, I wonder if you would tell us next about the interesting electrolyte disturbances that occur in the sweat, saliva and the tears in a patient with this disease, and the application of this information to the important diagnostic test, the so-called "sweat" test.

DR. MIDDELKAMP: The application dates back to 1952 at which time Dr. Dorothy Anderson at Columbia University, who actually first described this disease and its pathology in 1938, noticed that during the extremely hot summer in New York in 1948 a large number of patients with cystic fibrosis were admitted to the hospital and that most of them showed striking hyponatremia and hypochloremia which could not be explained on the basis of loss through the urine. Since the sweat glands enter into the physiologic picture in a major way during hot weather, the sweat of these patients was analyzed. It was found that the sweat chloride in patients with cystic fibrosis was greatly elevated over that found in normal persons. As a result of these findings the sweat test has become a diagnostic procedure utilized over all the country for the diagnosis of patients with cystic fibrosis. The mean chloride value for sweat in normal children is between 30 to 40 mEq./L. In patients with fibrocystic disease, the chloride concentration in sweat varies from a mean of 105 mEq./L. to as high as 125 mEq./L. as reported by different groups. The sodium concentration present in the sweat of normal children has been found to be around 60 mEq./L., while patients with cystic fibrosis have a mean of around 120 mEq./L.

With further studies, Dr. S. Bessman at the University of Maryland analyzed saliva and found that there was an increased secretory rate of the parotid gland as well as increased secretion of sodium and chloride in the saliva of these patients. An elevation of 10 to 15 mEq./L. of both sodium and chloride in the mixed saliva specimens from patients with cystic fibrosis over that from normal persons was found. A group from the University of Pennsylvania recently has been able to demonstrate that there is a similar elevation of sodium and chloride in the tears of persons with cystic fibrosis. At present, because 1 to 2 per cent of patients with cystic fibrosis do not have elevated sweat electrolytes, we still utilize duodenal drainage in conjunction with the sweat test to aid us in the diagnosis of cystic fibrosis. Unfortunately, the mechanism involved in the increased loss of sodium and chloride present in the sweat, saliva, and tears has not been clarified as yet.

DR. REINHARD: I would like to consider the complications of this disease, most of which are thought to be attributable directly or indirectly to obstruction of the secretory ducts or the passageways in the body by the very tenacious mucus. I would like to direct your attention first to the biliary system and the liver. Dr. di Sant Agnese of Columbia University reviewed the autopsy records at the Babies Hospital in New York from 1935 to 1955. There were 116 patients in this twenty-year period with fibrocystic disease of the pancreas, of these twenty-five had cirrhotic lesions of one sort or another. This is an

incidence of over 25 per cent. However, Dr. di Sant Agnese goes on to emphasize that usually the cirrhosis was a chance finding and had not produced any clinical symptoms. Dr. Shatz, what is the pathogenesis of the hepatic lesion in this disease?

DR. SHATZ: The lesions in the liver are thought to be the result of obstruction of the small bile ducts by the inspissated secretions, just as the pathogenesis of the pancreatic lesions depends on obstruction. The clinical complications are primarily those of portal hypertension rather than of hepatic insufficiency in patients who live long enough with this disease. As a result esophageal varices with hemorrhage are ultimately the most serious complication.

DR. REINHARD: It is often difficult to make a definitive diagnosis of cirrhosis in these patients although the liver may be enlarged due to biliary cirrhosis, it is also frequently enlarged due to the right-sided heart failure. Would you like to hazard a guess as to whether or not, hepatomegaly was due to biliary cirrhosis or cardiac failure in the patient under discussion?

DR. SHATZ: I would guess it was probably due to cardiac failure in this patient. Results of all the liver function tests were normal and there was no evidence of portal hypertension. I believe that all cases reported with biliary cirrhosis also had splenomegaly which this patient did not have.

DR. REINHARD: Could it have been a little bit of both? Dr. Klingberg?

DR. KLINGBERG: I would just like to mention that this picture of biliary cirrhosis is sometimes seen in the newborn and is one of the causes of jaundice occurring in the newborn. This is an intrauterine biliary cirrhosis.

DR. REINHARD: Next I would like to consider pulmonary complications of this disease which are extremely important. Dr. Noah, I believe that in these patients the same pulmonary lesions develop, as far as the complications are concerned, as in patients with long-standing severe bronchial asthma, or intrinsic asthma. I wonder if you would discuss briefly the pathogenesis of the lesions, and comment if there is any difference at all in what happens to these people and to patients with long-standing bronchial asthma in terms of the end result. What I have in mind particularly is, are there any cystic lesions in the lungs that cannot be explained on the basis of obstructive emphysema and secondary infection?

DR. NOAH: It is my understanding that the pathogenesis of lesions in the lung is essentially the same in persons who have primary mucoviscidosis and apparently become secondarily infected as in those who have some type of pulmonary infection eventually resulting in a great deal of viscid secretion which produces the bronchial obstruction. The lesions which are associated with obstruction produced by secretions include atelectasis, bronchiectasis and bronchopneumonia. The occurrence of these repeatedly in an infant is perhaps almost pathognomonic of mucoviscidosis. The further complications secondary to the infectious process are pulmonary fibrosis, which involves all lobes of the lung and, as a result, eventual pulmonary hypertension, cor pulmonale and cardiac failure.

DR. REINHARD: Dr. Middelkamp, I think there are some interesting features about the secondary pulmonary infections that occur in these patients. There appear to be certain organisms that are particularly common in these respiratory infections. Would you comment on this and the reason for it?

DR. MIDDELKAMP: Yes, Dr. Schwachman* and his group were able to recover the staphylococcus inpure culture from 44 per cent of their patients in whom postmortem examination was made. It had been postulated that staphylococcus grows best on media containing a higher concentration of salt than do other organisms; this has been suggested as the reason it is frequently isolated from patients with cystic fibrosis. However, with the use of prolonged prophylactic antibiotic therapy in these patients we now isolate from our patients pyocyaneus proteus organisms as the complicating pathogens present in the sputum.

DR. REINHARD: I was intrigued with this suggestion you mentioned. Knight, of Vanderbilt, reports that a medium containing 7.5 per cent sodium chloride is effective in isolating staphylococcus in mixed sputum cultures. The staphylococcus will continue to grow and all the other organisms tend to be inhibited by this salt concentration. Certainly the salt concentration in the saliva of these patients is higher than in normal people. Do you have any other comments regarding infection in this disease, Dr. Harford?

* SCHWACHMAN, H., LEUBNER, H. and CATZEL, P. Advances in Pediatrics. vol. 7, pp. 249–317. Chicago, Ill., 1955. Year Book Publishers, Inc.

DR. CARL G. HARFORD: I think it might be pointed out that there is a great deal of experimental evidence to show that mixing bacteria with mucin, particularly hog-gastric mucin, enable the bacteria to produce infection much more readily. It is often desirable to experimentally infect animals with pathogens which will infect human beings but ordinarily will not infect the experimental animal. It has been found that simply mixing the organisms with mucin will make this possible. I think the meningococcus is one of the best examples. Of course now it is a standard experimental method, for producing pneumonia in animals, to simply mix pneumococci with mucin and give the injection intrabronchially. This would fit in very nicely with the natural history of mucoviscidosis.

DR. REINHARD: That is quite interesting. I wonder, Dr. Klingberg, if you would comment in general on the effectiveness of therapy of respiratory disease, and particularly on the effectiveness of bronchodilators, expectorants and aerosols that are commonly used.

DR. KLINGBERG: In our experience these have not been of great benefit. Of most benefit has been the control of the bacterial infection with prolonged, and if you want to call it prophylactic administration of the drug, alternating from a one- or two-week period to the next one- or two-week period by changing the various drugs. This has prolonged life in a fairly good per cent of these children. The use of bronchodilators and other things has not been very satisfactory. Many times these children get into real difficulty, but we have found proper administration of fluids to thin down some of the mucoid secretions of greater benefit plus the use of moisturized oxygen.

DR. REINHARD: Dr. Middelkamp, do you believe the alternate use of different antibiotics is helpful?

DR. MIDDELKAMP: Yes, we found it fairly satisfactory although again there is marked individual variation and some patients can be maintained satisfactorily on a single antibiotic for a period of time. When an intercurrent infection with temperature elevation and other symptoms develops we usually take specific cultures and check antibiotic sensitivities to determine which antibiotic is the most effective for the specific infection.

DR. NOAH: I think the recent experience in treating the adult form of chronic pulmonary infection is showing a somewhat different result. Studies of patients treated with antibiotics over a long period of time, that is, patients with pulmonary emphysema or a similar form of chronic lung disease, have shown that broad spectrum antibiotics, particularly tetracycline, given in doses of as much as 1 gm. a day over a period of weeks and months have produced the most beneficial results.

DR. REINHARD: Any comment, Dr. Harford?

DR. HARFORD: In view of the fact that in other situations there is now controlled clinical evidence that antibiotic prophylaxis is not beneficial and may even be harmful, I wonder if Dr. Middelkamp and Dr. Klingberg think that this might be an exception to the rule?

DR. REINHARD: Certainly the general rule that prophylactic therapy is most effective when we have an organism that never develops resistance, such as the hemolytic streptococcus, would make me wonder whether prophylactic chemotherapy is indicated in this situation.

DR. MIDDELKAMP: I think Dr. Harford is right. I would say that over the past five years prophylactic antibiotic therapy had been carried out, but now there are occasionally reports of monilia infections occurring in this type of patient, too.

DR. KLINGBERG: Plus the occurrence of proteus and pyocyaneous infections which are certainly not very responsive to any of the agents used today.

DR. REINHARD: We can all agree that treatment of the respiratory complications of this disease are extremely unsatisfactory. Is that correct?

DR. KLINGBERG: This is certainly correct.

DR. REINHARD: In patients with this disease conditions are certainly ideal for the development of cor pulmonale. Dr. Royce of the University of Southern California has stated that approximately one-third of the children who die of fibrocystic disease have clinical evidence of heart failure at some time. I wonder, Dr. Nelson, if you would comment on the mechanism of heart failure and also on the prognosis when heart failure does occur in these patients.

DR. ROGER NELSON: There is no known direct effect of the mucoviscidosis on the heart and all the cardiac effects are secondary to the lung disease. The lung disease produces pulmonary hypertension which in turn causes right-sided heart failure. Pulmonary hypertension in these people, as in other patients with emphysema and bronchiectasis is due probably to a group

of factors including the decrease in the vascular bed of the lung and hypoxia of the pulmonary venous segment which produces pulmonary arteriolar constriction. This arteriolar constriction is mediated via mechanisms not fully understood—either a central nervous system reflex or a simple local venoarterial reflex or by a direct effect on the vessel wall. The hypervolemia that sometimes develops is also a factor, and finally there is an increase in bronchial arterial blood flow with enlarged bronchopulmonary anastomoses that develops with bronchiectasis. This refluxes blood at systemic pressure back into the low pressure pulmonary arterial system, thus elevating the pulmonary artery pressure. This pulmonary hypertension eventually results in cor pulmonale. The response of patients with obstructive emphysema and bronchiectasis once cor pulmonale develops is on the whole poor, especially in patients with mucoviscidosis.

Dr. Reinhard: Does anyone have any comments to add on the cardiac problem here?

Dr Shatz: Dr. Reinhard, would someone comment on the possibility that carbon dioxide narcosis was involved in the death of this patient? The CO_2 combining power was 46 mEq./L. before she died. She came in lethargic, and following the administration of sodium chloride the sodium level increased but the chlorides did not.

Dr. Reinhard: Yes. At least the patient had respiratory acidosis and this is a fairly common complication of this disease.

Dr. Sherry: I do not believe that we should conclude that the elevated CO_2 was due purely to a respiratory acidosis. There could have been a considerable amount of metabolic alkalosis secondary to a severe electrolyte loss, particularly of chloride, occurring in association with the diarrhea and sweating which the patient exhibited as a terminal event.

Dr. Reinhard: This patient really did not have much diarrhea during the latter part of her course and she died in March so we may assume she had not been sweating excessively.

Dr. Sherry: Except that these patients are known to be excessive salt losers and any manifestation which might cause loss of fluid could be associated with a marked salt loss.

Dr. Reinhard: That certainly is true. I think in this particular patient that the respiratory acidosis was the more important factor.

Dr. Sherry: I do not believe we should turn this case over to the pathologist without pointing out that internists formerly looked at mucoviscidosis as an interesting pediatric disease. Today patients with mucoviscidosis are beginning to survive into adult life. This may be due to better supportive therapy or to the fact that milder cases may go unrecognized; nevertheless we should be aware of its occurrence in adult life.

Dr. Reinhard: My final diagnoses therefore are: (1) mucoviscidosis with fibrocystic disease of the pancreas, (2) chronic pulmonary disease secondary to mucoviscidosis and pulmonary infection, (3) hepatomegaly probably due to a combination of mild biliary cirrhosis plus cardiac failure, and (4) early right heart strain secondary to the bronchiectasis and obstructive emphysema.

PATHOLOGIC DISCUSSION

Dr. Victor E. Rizk: The gross pathologic findings were quite consistent with the clinical impression. On external examination of the body there was evidence of marked emaciation as well as loss of subcutaneous fat. There was no fluid in the various serous cavities. The lungs were markedly emphysematous, filling the chest cavity and covering the pericardium anteriorally. There were multiple pleural adhesions on the right side, especially posteriorly and around the upper lobe of the right lung. Multiple areas of pulmonary parenchyma were reddish brown, firm, and slightly elevated. On cut surface these were found to be areas of intra-alveolar hemorrhage. The cut surface of the lungs showed definite thickening of the bronchial walls, and a large amount of thick, mucopurulent material which was plugging many of the bronchioles. There was no definite gross evidence of bronchopneumonia. The hilar lymph nodes were definitely hyperplastic and enlarged. The heart weighed 280 gm. It did not show any specific lesions. The liver weighed 1,080 gm. The capsule on the inferior aspect of the liver was slightly thickened, but there was no definite gross evidence of fibrosis in the liver. The gallbladder was small; it measured about 1 by 2 to 2.5 cm. and it contained mucoid, slightly greenish material. The common bile duct was patent and measured 0.5 cm. in diameter. Two hepatic ducts could be traced to the liver. The pancreas was definitely small and fibrotic, and showed marked fat infiltration. There were multiple 2 to 10 mm. cysts over the surface of the pancreas. A closeup view of the pancreas

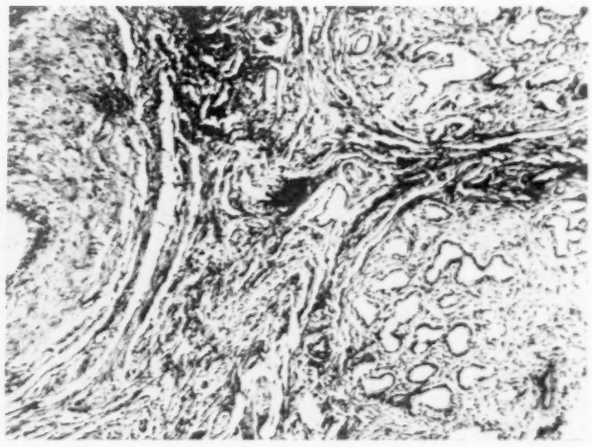


FIG. 1. Photomicrograph of the pancreas shows dense interlobular and intralobular fibrosis and fibrosis of the major pancreatic duct (left). No acinar tissue is recognizable in these lobules which consist entirely of dilated interlobular ducts. Hematoxylin and eosin × 45.

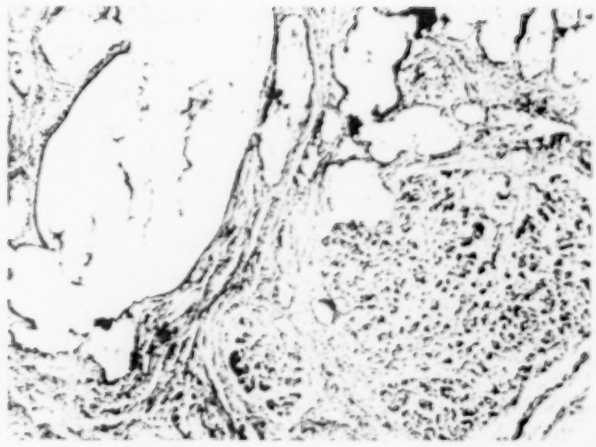


FIG. 2. A lobule of atrophic but still recognizable pancreatic acini adjacent to several epithelial lined cystic spaces containing bile-stained inspissated mucous. Hematoxylin and eosin × 45.

showed the cysts very clearly. Examination of the alimentary tract showed no specific lesions; the mucosa looked normal. The esophagus showed esophagomalacia, which was thought to be terminal. The rest of the organs did not show any specific lesions; the spinal column, I may add, showed kyphosis as well as scoliosis to the right in the upper part of the column.

JOHN M. KISSANE: Dr. Rizk has described the gross pathologic features of this disease which are highly characteristic in a long-standing case. This is then, a case of fibrocystic disease with severe involvement predominantly of the pancreas and respiratory tree. The first photomicrograph (Fig. 1) shows a section from the body of the pancreas. These lobules are encased in dense fibrous tissue, and many lobules consist entirely of dilated ramifications of terminal interlobular ducts, the acini having undergone complete atrophy. The epithelium of these ducts is flattened, atrophic and focally cystically dilated. In the less severely involved lobules, atrophic acini can still be recognized. (Fig. 2.) This major pancreatic duct is dilated and fibrotic. In the fibrous tissue adjoining the pancreas, one can identify ducts and persistent pancreatic islets, the only remnants of pancreatic tissue in which the acini have been completely obliterated.

The duodenal mucosa is involved as well as

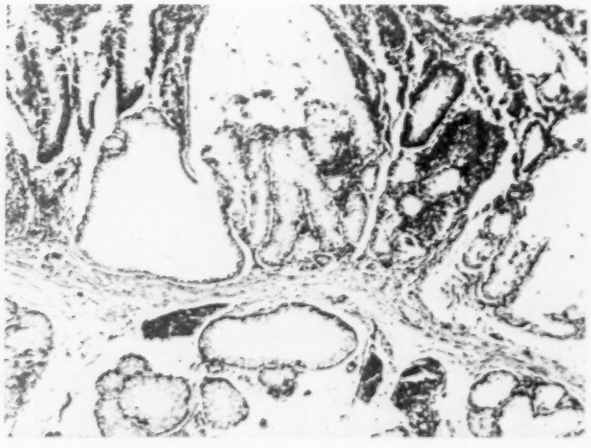


FIG. 3. The duodenal mucosa shows dilated crypts and dilation of Brunner's glands. Hematoxylin and eosin × 90.

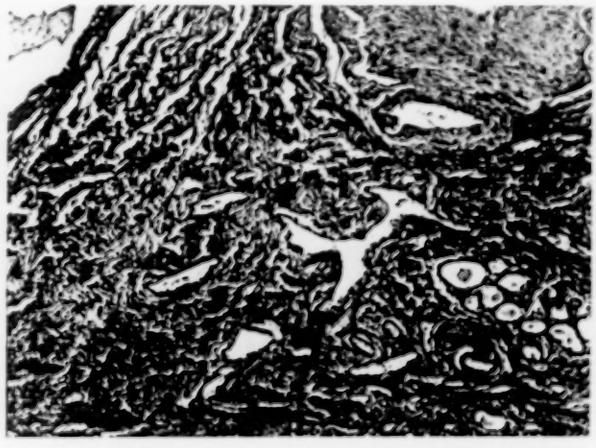


FIG. 4. A bronchial lumen (upper left) contains inspissated mucous. The wall is markedly fibrotic. Cystic dilatation and atrophy of epithelium are evident in the bronchial submucous glands (lower right). Hematoxylin and eosin × 150.

the pancreas. Atrophy and cystic dilatation is evident in Brunner's glands, and, as in the pancreas, this involvement follows essentially a lobular distribution. The overlying mucosa is similarly involved as one sees in the cystic dilatation of the mucosal crypts. (Fig. 3.)

Dr. Rizk described focal thickening of the capsule of the liver. In sections from such foci, one can identify nests of epithelial cells in subcapsular fibrous scars. In the depths of the liver is a slight increase in periportal fibrous connective tissue, especially for a girl of seventeen years. Some of the smaller bile ducts were dilated, but there were no true cysts. In the lungs, alternating areas of extreme over expansion of alveoli and areas of collapse with interstitial fibrous scarring are evident. Bronchi are dilated, show foci of squamous metaplasia and, contain both an acute and chronic inflammatory infiltrate in their walls. Pathologically, differentiation of this process from bronchial asthma is not difficult because, although superficially the bronchial inflammation, peribronchial fibrosis and lobular emphysema may resemble the picture in asthma, the involvement of submucous glands in the respiratory tract in cystic fibrosis is the opposite of that in asthma. In asthma, the submucous glands appear succulent and hyperactive, whereas in this disease, they are involved in the atrophy and cystic dilatation seen in other eccrine glands. (Fig. 4.)

Higher magnification of smaller bronchi shows focal squamous metaplasia and characteristic basophilic mucous in the lumen. In the pulmonary parenchyma itself, one finds areas of dense fibrous scarring with foci of cuboidal bronchiolar metaplasia in surrounding alveoli.

Microscopically, there was little actual pneumonia in small scattered foci; the predominant picture is a chronic bronchitis and bronchiolitis.

Other organs which may be involved, such as the salivary glands, were not available to us because of a limited autopsy permit. The sweat glands, as has usually been the case, were normal histologically. This makes the point, however, which has been made in the recent literature devoted to this disease that, for a disease with morphologic alterations of serous salivary glands, and chemical derangement of the eccrine sweat glands, the term mucoviscidosis is too limited a designation emphasizing as it does, only the alteration in mucous-secreting glands while the disease actually appears to represent an abnormality of several type of glands throughout the body.

The anatomic findings were: fibrocystic disease with involvement of eccrine glands of the pancreas, duodenum, and bronchi; atrophy of acinar tissue of the pancreas, advanced; subcapsular and periportal fibrosis of the liver, slight; acute and chronic tracheobronchitis, advanced; bronchiectasis, moderate, predominantly in the lower lobes; pulmonary emphysema, advanced; focal bronchopneumonia, slight; intraalveolar hemorrhages in the left lung and lower lobe of the right lung; hyperplasia of the tracheobronchial lymph nodes; emaciation (40 kg.) and esophagomalacia.

Case Reports

Chronic Cor Pulmonale Due to Multiple Pulmonary Emboli and Accompanied by Diffuse Interstitial Fibrosis*

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THERE are frequent reports in the literature of patients with multiple pulmonary emboli resulting ultimately in death from right ventricular failure [*1–10*]. The case to be reported is of interest because of clinical features which required extensive diagnostic studies and the infrequently reported finding of diffuse interstitial fibrosis of the lungs accompanying multiple pulmonary emboli.

CASE REPORT

L. B., a thirty-seven year old Negro man, was first seen in the Receiving Ward of the Pennsylvania Hospital in May 1955. He complained of shortness of breath and ankle edema of six month's duration. There was a one-day history of stabbing pain in the chest, dizziness and increase in exertional dyspnea. Significant physical findings at that time were: shortening of the left leg, a residual of poliomyelitis; a split second sound in the pulmonic area; a questionable gallop rhythm; and enlargement of the liver. On an outpatient visit the above findings were confirmed and, in addition, apical diastolic and presystolic murmurs were heard, leading to the impression of mitral stenosis. Significant laboratory findings were a hemoglobin of 8.5 gm. per cent and a urinalysis showing a trace of albumin, pus cells and bacteria. X-ray film of the chest revealed an area of density above the right diaphragm. He was referred to the Chest Clinic on August 11, 1955, at which time he had the additional symptoms of cough and an occasional small hemoptysis. Rales were noted in the right apex and base. The murmur of mitral stenosis was heard again. A chest roentgenogram (Fig. 1) showed densities in the right apex and base and a lesion in the left hilum, subsequently suspected of being a dilated left pulmonary artery. Results of acid-fast studies were negative. Antibiotics were administered. A repeat roentgenogram of the chest on August 30 showed slight clearing of the shadow on the right side.

The patient was next seen in March 1957 complaining of increased exertional dyspnea. A "ruddy" pigmentation of the face was noted. Cardiac auscultation failed to confirm the diastolic murmur. The liver was still enlarged. The spleen was not felt. An X-ray film of the chest (Fig. 2) showed "emphysema of the left upper lobe," dilatation of the main pulmonary trunks suggesting pulmonary hypertension, and marked cardiac enlargement, greater than that of August 1955. Figure 3 shows electrocardiograms representative of those throughout his course. To be noted are a progressive shift of the electrical axis to the right and increasing evidence for right ventricular hypertrophy.

The patient was admitted to the hospital on March 28, 1957, for further study. Admission laboratory data were: a hypochromic anemia with 10.2 gm. per cent hemoglobin and 40 per cent hematocrit; normal white blood cell count and differential; negative sickle cell test; and a normal urinalysis. Liver function studies were within normal limits except for an alkaline phosphatase of 10.1 Bodansky units and a prothrombin time of 52 per cent. Fluoroscopy confirmed the findings on X-ray film noted two weeks earlier. A "hilar dance" was not seen. Cardiac catheterization was performed. (Table 1.) To be noted is elevation of the pulmonary artery and right ventricular pressures with a normal "wedge" pressure. There was no evidence of a left-to-right shunt and arterial unsaturation was noted. However, a repeat determination showed 94 per cent saturation

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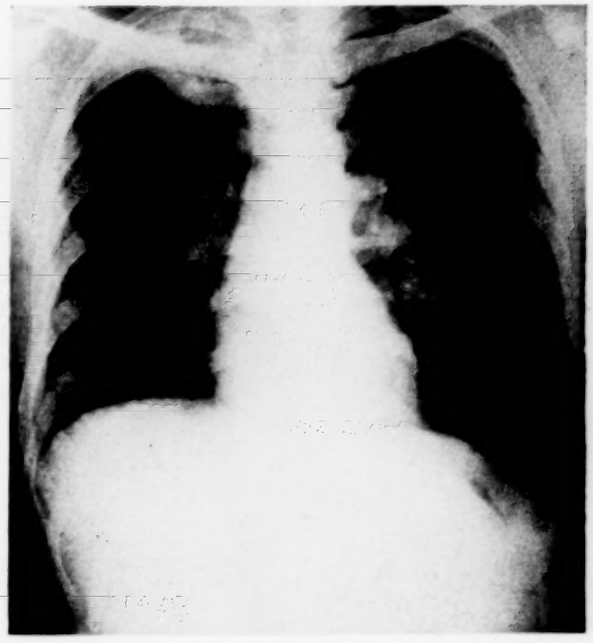


FIG. 1. Chest roentgenogram on August 24, 1955. Densities present in right apex and base. Increased prominence in left hilum due to dilated left pulmonary artery.

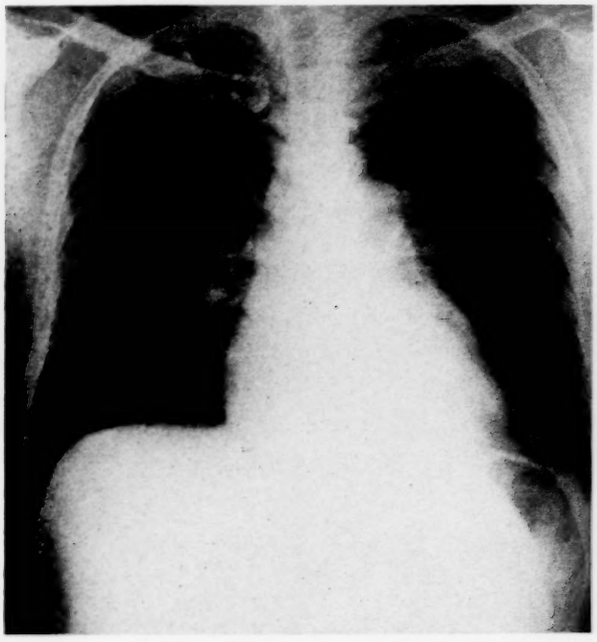


FIG. 2. Chest roentgenogram on March 15, 1957. Cardiac enlargement with prominence of pulmonary artery segment and main pulmonary trunks. Radiolucency of lobe of left lung.

with the patient breathing room air, rising to 99.5 per cent with 100 per cent oxygen. The cardiac output was decreased and the total pulmonary resistance increased due to elevation of the pulmonary arteriolar resistance. Although the specific cause for the pulmonary hypertension was not clear, it was believed that an intracardiac shunt had been excluded and that pulmonary disease such as fibrosis or emboli was responsible. Consideration was given to the diagnosis of malignant carcinoid because of the finding of pulmonary hypertension and a somewhat atypical pigmentation of the face. Two determinations of the urinary 5-hydroxyindol acetic acid, however, were negative. Preliminary pulmonary function studies corresponded closely to those shown later. Biopsy of the lung was performed and reported as showing interstitial fibrosis, hyaline membrane formation, interstitial pneumonitis and moderate hemosiderosis, findings thought to be consistent with the diagnosis of the Hamman-Rich syndrome. Administration of prednisone, 30 mg. daily, was begun and continued for a period of two and a half weeks, without significant effect.

Following discharge from the hospital he continued on a progressively downhill course until the time of his final hospital admission. There were two interim admissions to the hospital: one for anticoagulant therapy of a thrombophlebitis, thought secondary to an injection of Decholin®; and one for control of congestive heart failure. Dicumarol therapy with prothrombin times in the range of 20 to 30 per cent was continued until the time of his death five months later. There was a persistence of his hypochromic microcytic anemia with a normal bone marrow and negative stool guaiac.

On October 9 he was referred to the University of

TABLE 1
CARDIAC CATHETERIZATION *

Cardiac Site	O_2 Content (volumes %)	Pressure (mm. Hg)	
		S/D	Mean
"Pulmonary capillary"	.....	13/9	10
Right pulmonary artery	6.65	68/26	41
Main pulmonary artery	.....	72/32	..
Right ventricle	6.51	68/21	38
Right atrium	7.22	...	13
Superior vena cava	7.46	19/11	15
Brachial artery	12.35 (87.9%)	...	..
Arterial capacity	14.08	...	..

* Cardiac output: 3.2 L./minute.
Cardiac index: 1.97 L./minute/M^2.
Total pulmonary resistance: 1020 dynes second/cm^5.
Pulmonary artery resistance: 760 dynes second/cm^5.
Arterial O_2 saturation: on room air 94.0 per cent on O_2 10 minutes 99.5 per cent.

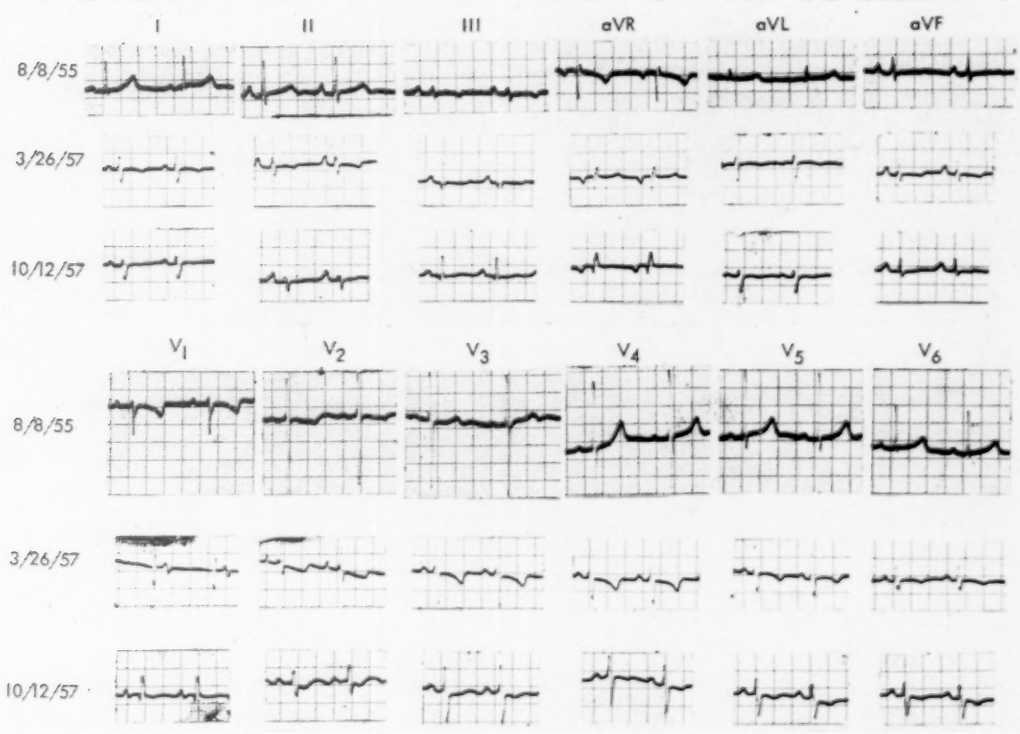


FIG. 3. Serial electrocardiograms. August 8, 1955: Inverted T waves in leads V1 and V2 consistent with right ventricular hypertrophy. March 26, 1957: Electrical axis has shifted to the right accompanied by further T wave abnormalities in precordial leads over the right ventricle. October 12, 1957: Further shift of the axis to the right and development of pattern of right ventricular hypertrophy.

Pennsylvania Hospital where further pulmonary function studies were performed. (Table II.) The lung volumes were only slightly abnormal. There was a slight reduction in maximal flow rates, timed and total vital capacity and maximum breathing capacity. There was a low normal lung compliance and normal airway resistance. The diffusing capacity of the lungs was markedly reduced. The presence of a normal lung compliance and pulmonary mechanics associated with a marked decrease in diffusing capacity was interpreted as being compatible with multiple pulmonary emboli or primary pulmonary hypertension. Extensive alveolar wall fibrosis was considered unlikely in the presence of a normal lung compliance.

TABLE II
PULMONARY FUNCTION STUDIES

Pulmonary Function	Normal	Patient
Inspiratory capacity	3000 cc.	2060
Expiratory residual volume	1000 cc.	1010
Vital capacity	4000 cc.	2680
Residual volume	1200 cc.	1490
Total lung capacity	5200 cc.	4170
Functional reserve capacity	2200 cc.	2500
Maximinal expiratory flow rate	400 L./min.	216
Maximal inspiratory flow rate	300 L./min.	206
% Vital capacity 1 second	81	68
% Vital capacity 3 seconds	95	93
Maximum breathing capacity	113 L./min.	77
Compliance	.14–0.28 L./cm. H_2O	.14
Airway resistance	0.5 –1.5 cm. H_2O/L./sec.	1.07
Index of intrapulmonary mixing	2.0%	0.5– 0.2
Diffusion capacity for O_2	25 ± 7 cc./min./mm./Hg	9.6–11.0

The final hospital admission was on October 11. The only significant laboratory finding was a rise in hemoglobin to 14 gm. per cent with a hematocrit of 52. His status remained unchanged until October 19 when a marked increase in dyspnea developed. A chest roentgenogram taken five days before, although unchanged from previous films, which were not available for comparison, was interpreted as showing a pneumothorax of the upper lobe of the left lung. An attempt to relieve the "pneumothorax" by aspiration resulted in the development of a tension pneumothorax and sudden death.

At autopsy a pneumothorax was present in the left hemithorax with atelectasis of the left lung. A large thrombus was seen in the left pulmonary artery. (Fig. 4.) The thrombus almost obliterated the lumen, adhered tightly to the internal surface of the artery, and extended into the upper lobe branch preventing blood flow to this portion of the lung. This thrombus

was thought to be of embolic origin although its source was not apparent at autopsy. Multiple pulmonary thrombi were seen in various stages of organization in the smaller arteries. Cut sections of the lung showed diffuse, patchy, gray areas, more extensive in the right lung than the left, which on microscopic examination were found to be due to interstitial fibrosis. The heart weighed 440 gm. The right ventricle showed dilatation and hypertrophy, its wall measuring 8 mm. The left ventricle showed slight hypertrophy, but no dilatation, measuring 12 mm. The right atrium was enlarged and its endocardial surface was thickened. The valves were normal. There were no thrombi in any of the chambers. Additional findings were: hypertrophic gastritis, central hemorrhagic necrosis of the liver, and generalized visceral congestion.

Figure 5 is a photomicrograph of a section from the lower lobe of the right lung showing marked intimal thickening in an arteriole with surrounding atelectasis and interstitial round cell infiltration. Figure 6 shows an organized thrombus with recanalization. Another section (Fig. 7) shows prominent alveolar cells of cuboidal appearance, interstitial round cell infiltration and spotty interstitial fibrosis. Another section, not shown here, revealed patchy areas of interstitial fibrosis in juxtaposition to relatively normal alveoli. The pattern of healed pulmonary infarction was not seen, a finding mentioned previously by Castleman [*11*] and Smith [*34*].



FIG. 4. Left lung with left pulmonary artery opened showing large thrombus lodging in the lumen.

COMMENT

The problem of diagnosis and treatment of the patient suspected of having embolic phenomena to the lungs is usually frought with difficulties.

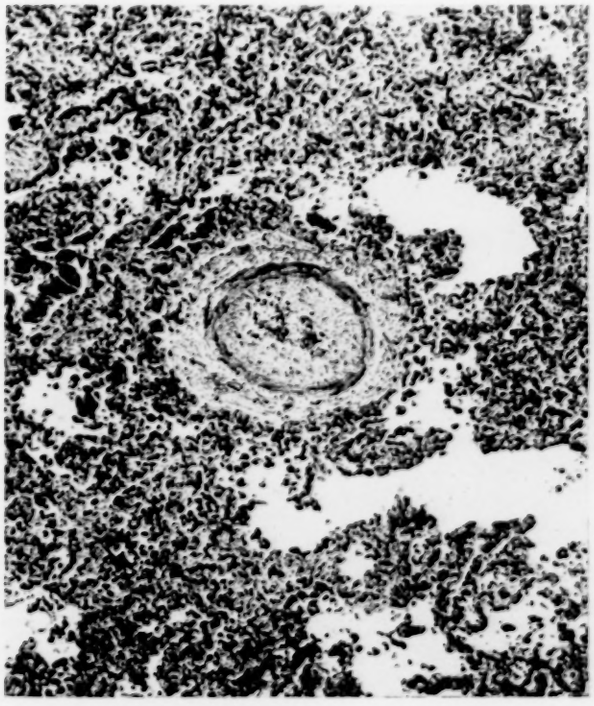


FIG. 5. Section from lower lobe of right lung. Marked intimal thickening of arteriole and surrounding atelectasis. Original magnification × 60.



FIG. 6. Upper lobe of left lung. Organized thrombus with recanalization. Original magnification × 60.

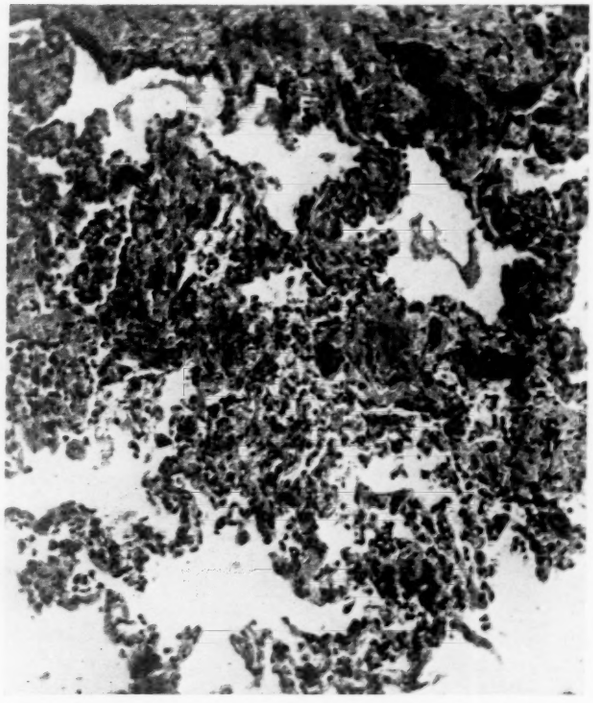


FIG. 7. Lower lobe of right lung. Cuboidal alveolar cells, round cell infiltration and interstitial fibrosis. Original magnification × 43.

It is a life-threatening complication arising from an otherwise benign condition. When the diagnosis is in doubt such procedures as inferior vena cava ligation and long-term anticoagulant therapy are not entered into lightly. In this particular case the clinical diagnosis of pulmonary embolus was not established until autopsy. In fact, the lung biopsy revealed an additional process, confirmed at autopsy, i.e., the interstitial fibrosis.

The picture of interstitial fibrosis described in this case meets the histologic criteria of the syndrome originally described by Hamman and Rich [*12,13*] and subsequently identified by numerous others [*14–26*]. These changes consist of an early stage in which there is an insignificant inflammatory alveolar exudate consisting of albuminous fluid, red blood cells and polymorphonuclear leukocytes. The septal walls of the alveoli are enlarged, become cuboidal and in some places desquamate leaving a hyaline membrane. Later fibroblastic proliferation takes place in the alveolar walls and into the hyaline membrane with little organization taking place in the alveoli themselves. A few inflammatory cells consisting of lymphocytes, histiocytes and occasional eosinophils are seen in the interstitial areas. This process of fibrosis continues to an end stage of dense hyaline connective tissue in which fibroblasts have disappeared and the elastic tissue has become clumped.

King [*27*], quoting Nelson and Heublein, has given a complete classification of pulmonary fibrosis, pulmonary infarction being included. Andrews [*28*] mentions five cases of diffuse interstitial fibrosis secondary to pulmonary vein obstruction in which medial hypertrophy and intimal proliferation of the arterioles and small arteries were found and attributed to thrombi in some of these vessels. He states that such thromboses did not play a primary etiologic role in the development of fibrosis since thromboses do not produce interstitial fibrosis of the type seen in these patients. In our patient there was no gross evidence of pulmonary vein obstruction at autopsy. Mallory [*29*] divides pulmonary fibrosis into five etiologies, distinguishing between fibrosis due to healed infarction and interstitial fibrosis. He states, however, that "though multiple foci of healed infarction due to embolism are theoretically a possible cause of diffuse pulmonary fibrosis, it is improbable that many patients survive the acute stage of the disease. Only one case in the present series was attributable to this mechanism. It might be supposed that the more slowly developing vascular occlusion of idiopathic pulmonary arteriosclerosis (Ayerza's disease) would be more likely to produce widespread injury to the pulmonary parenchyma; yet in only 1 of 6 cases were significant patches of fibrosis noted." It is possible that the changes he ascribes in this one case to Ayerza's disease may also be found in patients who survive multiple pulmonary infarcts inasmuch as this is now a recognized cause of Ayerza's disease. Although the findings of healed pulmonary infarction as described by Castleman [*11*] were not found in the present patient, it is possible that the diffuse interstitial fibrosis thought to be a separate and idiopathic process may indeed have been due to the vascular occlusions, an infrequently mentioned feature. Functionally, however, the fibrosis played a secondary role in this patient's disease process.

The question of whether or not we are dealing with a case of primary pulmonary artery thrombosis should be raised. The distinction between this and pulmonary embolism by the histologic findings is difficult [*2,11*]. Belt [*3*] lists eight differential features but Brewer [*30*] states that, except in cases of acute pulmonary arteritis, syphilitic arteritis, and aneurysm of the pul-

monary artery, cases of pulmonary artery thrombi are in reality due to embolic obstruction of small branches with later superimposed retrograde thrombi. However, the situation becomes even more complex if one accepts Dexter's [*37*] concept that pulmonary hypertension with resulting right ventricular failure and diminished pulmonary blood flow may lead to the development of *in situ* pulmonary thrombosis. In our patient, although no obvious thrombophlebitis was found, the residual paralysis of the left leg may well have been a predisposing factor. In this connection it is of interest that Byrne *et al.* [*31*] list hemiplegia, after cardiac and postoperative situations, as this third most common predisposing cause for fatal pulmonary emboli.

The cardiac auscultatory findings are also of interest. The presence of a systolic murmur, split or loud P_2 or gallop rhythm has been mentioned frequently in previous reports [*2,4–8*]. However, a diastolic "mitral stenosis" murmur has been recognized in only two other patients [*5,32*] besides ours. In one patient [*5*] a right atrial thrombus was found at autopsy. No explanation was given for this murmur in the other patient nor was its transient appearance in ours readily explained. One may invoke the hypothesis used by Black and Harken [*33*] to explain the dynamic features of tricuspid stenosis found at cardiac catheterization of some patients with mitral stenosis where no tricuspid lesion was found at operation. This was explained by dilatation of the right ventricle causing the tricuspid valve to become stretched and its orifice slit-like, returning to normal when the right ventricular pressure was reduced by mitral commissurotomy. Perhaps our patient had a transient dilatation of the right ventricle at the time of one of his embolic episodes. Another possibility is that a right atrial thrombus had formed at one time but subsequently became dislodged so that it was no longer present at autopsy.

When the process is suspected by history and physical examination the following aids may be helpful to establish the diagnosis: (1) The establishment by cardiac catheterization of pulmonary hypertension with a normal wedge pressure. (2) Roentgenograms of the chest showing (a) diverse patterns suggestive of "complete or incomplete" infarction [*34,35*] and (b) decreased density of the pulmonary vascular markings peripheral to the point of vascular occlusion [*1,2*]. (3) Demonstration of major vessel obstruction by angiocardiography [*2,8,36*] and (4) Detailed cardiopulmonary function studies which may distinguish between vascular and parenchymal disease.

Therapy of recurrent pulmonary emboli is at present limited to venous ligation or anticoagulants. However, as in this patient, once pulmonary hypertension is established the course is usually a downhill one. Direct surgical attack on the occluded vessel has been attempted but autopsied cases have shown [*1,5*] that there is usually associated diffuse vessel obstruction. Unless the occlusion is recent, organization and extension of the thrombus would make its surgical removal difficult. Recent studies by several investigators in the field of enzymatic fibrinolysis for thromboembolic disease appear to offer another possible clinical approach [*38*].

SUMMARY

1. A patient with cor pulmonale with progressive right ventricular failure due to multiple emboli is reported.

2. A secondary feature was a spotty interstitial fibrosis first discovered by lung biopsy and confirmed at autopsy.

3. The cause of the interstitial fibrosis and its relationship to the vascular occlusion is discussed.

4. Studies which may be helpful in establishing the diagnosis of this disorder are listed.

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Dissecting Aneurysm of the Aorta Treated Surgically*

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DISSECTING aneurysm of the aorta is an acute and fatal disease with notable exceptions. For many years the diagnosis was beset with difficulties but, with increasing awareness of the condition and the availability of more precise diagnostic methods, dissecting aneurysms are now being recognized more often. Lately, a number of attempts have been made to treat the disease surgically. The following case report is added to a slowly accumulating experience with this treatment.

CASE REPORT

S. L., a sixty-two year old white shopkeeper, suddenly had severe pain in the back of the chest which quickly became agonizing. He was taken home immediately and given a hypodermic of Demerol.® During the night the patient was given two more injections of Demerol and oral sedation to control the pain. The following morning, March 23, 1958, the patient was admitted to another hospital. By this time the pain in the back had extended to the front of the chest, neck and abdomen. The patient had a temperature of 102°F. and weakness but no other localizing symptoms. The pain in the chest abated somewhat under sedation and became more localized in the abdomen.

The past history revealed that the patient had been afflicted for many years with psoriasis and psoriatic arthritis, chiefly involving the hands. The patient had also been treated with quinidine for episodes of paroxysmal auricular fibrillation. At various times he had received corticosteroids and salicylates. The administration of steroids had been discontinued several months previously but the day prior to the present illness the patient received an intramuscular injection of triamcinolone because of recurrence of painful swelling of the hands. In February 1957 the patient had been hospitalized because of suspected gastrointestinal bleeding. X-ray examination of the gastrointestinal tract and barium enema had failed to reveal any abnormalities. A chest roentgenogram on this occasion showed enlargement of the heart and widening of the aorta.

Because of the previous history of possible gastrointestinal bleeding and recent steroid medication, it was suspected at this time that the patient may have sustained perforation of a gastric ulcer. Roentgenograms of the abdomen failed to disclose free air. During the following three weeks roentgenograms of the gallbladder and upper gastrointestinal tract, as well as a cholangiogram were taken, and intravenous pyelography was performed in an effort to determine the cause of the pain and the persistent fever. During one of the abdominal examinations, cardiac enlargement was noted and a follow-up chest roentgenogram showed a density in the left hilar region which was suspected of being either a neoplasm, possibly a lymphoma, or a vascular mass. Except for the presence of moderate anemia and leukocytosis, the laboratory examinations were within normal limits.

On April 10, 1958, the patient first came under our observation. Examination revealed an apprehensive man who appeared acutely and chronically ill. There was patchy psoriasis of various parts of the skin and a deforming arthritis of the hands. There were no palpable lymph nodes or signs of venous engorgement. The heart was enlarged, A_2 greater than P_2. A loud systolic murmur was heard over the entire precordium, radiating to the neck and axilla. The blood pressure was 175/110 mm. Hg. The lungs were clear to percussion and auscultation. X-ray film of the chest showed enlargement of the heart. A density with a sharp outer margin was seen to the right of the trachea. The arch of the aorta revealed sclerotic changes and the descending thoracic aorta showed considerable widening. (Fig. 1.) Closer questioning revealed that the pain had been most severe initially in the lower left side of the back. In view of the intensity of the initial seizure and its location, as well as the appearance of the chest roentgenogram, a dissecting aneurysm of the aorta was suspected and the patient was transferred to Montefiore Hospital the same day.

The physical examination at this time confirmed the findings noted previously with the addition that on auscultation the loud systolic murmur heard over the precordium was also audible in the interscapular region and low down along the left thoracic spine. Blood pressure in the right arm was 160/100 mm. Hg;

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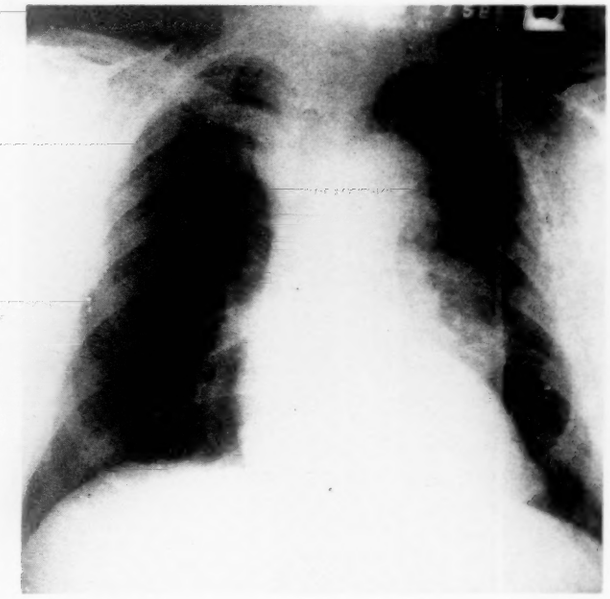


FIG. 1. Dissecting aneurysm of arch and descending aorta. Frontal conventional roentgenogram reveals marked widening of descending aorta; sclerotic plaque in aortic arch; density to the right of the trachea; enlarged heart.



FIG. 2. Frontal angiocardiogram reveals the heart, ascending and descending aorta opacified; non-opacified density lateral to opacified descending aorta; right paratracheal density caused by dilatation of inominate artery; tip of catheter in right atrium.

in the left arm, 170/100 mm. Hg; pulse 106, occasional extrasystoles, respiration 36. The abdomen was obese but not tender and a ventral hernia was present. The liver was palpable 3 fingerbreadths below the right costal margin. The femoral pulses were felt bilaterally, as were those of the popliteal, dorsalis pedis and posterior tibial arteries.

The laboratory examinations included: urinalysis, specific gravity 1.012, no albumin or sugar, 8 to 15 red blood cells; hematocrit, 40 per cent; white blood cells, 11,900 per cu. mm. with a normal differential; sedimentation rate, 85 per cent; fasting blood sugar, 91 mg. per cent; blood urea nitrogen, 20.8 mg. per cent; amylase, 84 mg. per cent; alkaline phosphatase, 3.1 mg. per cent; serum albumin, 3.3 gm. per cent; globulin, 3.4 gm. per cent; serum transaminase, 70 units; serum calcium, 9.5 mg. per cent; potassium, 4.5 mg. per cent; uric acid, 6.5 mg. per cent; and serum bilirubin, 0.87 mg. per cent. The cephalin flocculation test was negative; thymol turbidity test, 4 units; serologic test, negative; and blood cultures, negative.

On the night of admission to Montefiore Hospital the patient had an acute seizure of paroxysmal auricular fibrillation which was treated with digoxin. The electrocardiogram revealed a left ventricular hypertrophy pattern and auricular fibrillation alternating with regular rhythm. The blood pressure dropped to 120/80 mm. Hg. The pain in the lower left side of the back reappeared with increasing severity. During the following seventy-two hours the blood pressure rose and was more often higher in the right arm than in the left. With the administration of sedatives, digoxin and reserpine, the patient's acute symptoms slowly subsided.

A more specific test was then made to confirm the diagnosis of a dissecting aneurysm. On April 13, 1958, an angiogram was taken following injection of 50 cc. of 70 per cent Urokon* into the antecubital vein. The superior vena cava appeared compressed, narrowed and deviated toward the right with some filling of the azygos vein. There was no satisfactory opacification of the right side of the heart. There was reflux of dye into the neck and arm vessels indicating obstruction of the superior vena cava. The thoracic aorta was not visualized. Four days later a selective angiocardiogram was taken following rapid injection of contrast medium through a catheter introduced into the right atrium by way of a left femoral vein cut-down. Below the level of the great vessels there was marked widening of the descending aorta, extending down to the level of the diaphragm where the vessel appeared to bulge. The main aortic channel was well opacified with a non-opacified density measuring 4 cm. in width and paralleling the main channel. (Fig. 2.) The prominence noted in the right paratracheal region in the conventional chest roentgenogram appeared to be an aneurysmal dilatation of the inominate artery.

On April 22, 1958, left thoracotomy was performed with the patient under endotracheal general anesthesia and hypothermia to lower the temperature so that the aorta could be cross-clamped with minimal danger of renal failure and spinal cord degeneration



FIG. 3. Aorta cross-clamped proximally and distally. Opening shows true lumen of aorta much smaller in size than of entire aortic circumference.



FIG. 4. End-to-end anastomosis of transected aorta.

due to ischemia. The operation was begun after one hour when the patient's temperature reached 93°F. The sixth rib was removed subperiosteally and the pleural cavity entered. The descending thoracic aorta was found markedly dilated and elongated. There was considerable injection and inflammatory reaction of the parietal pleura overlying the thoracic aorta. The mid-portion of the thoracic descending aorta was mobilized by opening the parietal pleura over the aorta and dissecting the aorta off its bed. Two pairs of intercostal vessels were ligated and divided permitting mobilization of a 3 inch segment of aorta. The aorta was then cross-clamped with two long straight DeBakey clamps, and divided.

The lumen of the aorta revealed an intramural hematoma occupying the anterolateral one-third of the diameter of the aorta. The dissected segment contained fresh blood and some clotted blood. (Fig. 3.) The clots were removed proximally and distally from the outer dissected segment. The dissected channel was obliterated in the distal end of the transected aorta by a running No. 4-0 silk arterial suture approximating the adventitia to the intima of the vessel. A V-shaped segment of intima and media on the proximal end of the transected aorta was excised for a distance of 1 inch proximally, creating a fenestration in the dissected segment through which the blood flow could re-enter the main lumen of the aorta. The transected ends of the aorta were anastomosed end-to-end with continuous No. 4-0 arterial sutures anteriorly and posteriorly tying the sutures at opposite poles of the aorta. After the anastomosis was completed the distal aortic occluding clamp was slowly removed. There was no leakage of blood from the site of the anastomosis. The proximal aortic clamp was then slowly removed and circulation re-established to the distal aorta. (Fig. 4.) The site of the anastomosis was wrapped with Gelfoam® for added support.

The time during which the thoracic aorta was cross-clamped and circulation to the distal aorta stopped was twenty-nine minutes. During the operation the patient's temperature drifted from 93° to 89°F. where it remained stationary. During the period of cross-clamping of the aorta, the pulse rate slowed to 35 per minute. The systolic blood pressure rose precipitously to a range between 200 to 250 mm. Hg and diastolic pressure, 100 to 120 mm. Hg. The pulse remained strong; the cardiac rhythm regular. When the cross-clamp was removed the pulse rate returned to 65 to 70 per minute. A tube was placed in the thoracic cavity through the eighth interspace in the mid-axillary line and attached to underwater drainage with suction. The patient was taken from the operating room in good condition.

Histologically the excised specimen from the fenestration revealed a portion of arterial wall in which all the layers, especially the medial portion and intima, were involved by numerous atherosclerotic plaques. One portion of tissue represented an antemortem thrombus in the false passage.

Postoperatively the patient did well except for a period of hypotension which responded to blood replacement. After the operation the intensity of the systolic murmur over the precordium and in the left interscapular region diminished noticeably. On the second postoperative day the patient became disoriented. At this time it was discovered that for some years the patient had been under the care of a psychiatrist and the present episode was ascribed to a toxic psychosis. The patient's condition improved and he was discharged on May 9, 1958.

The patient did well at home while taking Thorazine® medication; he walked about in moderation, ate regularly but complained of epigastric pain. A week after his return home the patient noted small amounts of bright red blood in the stool. On May 25, 1958, he was awakened from sleep with a coughing spell and spat up a considerable amount of bright red

blood. He did not complain of pain in the chest. The patient was readmitted to Montefiore Hospital on May 25, 1958, agitated but without localizing complaints. Physical examination revealed the same harsh systolic murmur over the entire precordium heard previously. Blood pressure was 150/100 mm. Hg. The lungs were clear to percussion and auscultation. The abdomen was soft and no masses were felt. A few hours after admission the patient vomited about 100 cc. of gastric contents containing dark brown blood. For a time the patient felt better and was fully reactive. However, his blood pressure kept mounting, reaching 220/130 mm. Hg in six hours at which time he uttered a few gasps and died. It was suspected that the cause of death was proximal extension of the dissection possibly involving the pericardium and causing heart tamponade. An autopsy was not performed.

TEN PATIENTS PREVIOUSLY REPORTED ON AND TREATED SURGICALLY

The first patient, described by Gurin, Bulmer and Derby in 1935 [*1*], was a forty-three year old man in whom acute arterial occlusion of the right lower extremity developed. Two and a half hours after the onset of symptoms the abdomen was explored and a dissecting aneurysm was found occupying the right external iliac artery 3 inches above Poupart's ligament. After applying rubber padded clamps to the right external iliac artery, the intima and media were incised from within the vessel and a clamp inserted through this incision. The blood in the aneurysm was allowed to communicate with the main channel and the circulation in the extremity was restored. The patient died on the sixth postoperative day with signs of pneumonia and uremia.

Johns [*2*] described a fifty year old man with hypertensive heart disease. Twenty-four hours before admission to the hospital the patient had sharp pain in the lower left part of the abdomen and he shortly went into collapse. The preoperative diagnosis was retroperitoneal hemorrhage. The patient died in uremia on the eighth postoperative day. At autopsy a dissecting aneurysm of the abdominal aorta was found extending into the iliac artery with perforation.

Shaw [*3*] described a fifty year old man in whom squeezing, substernal pain developed suddenly. One hour later the patient had paralysis and anesthesia of both lower extremities. At operation an aneurysm was found in the lower abdominal aorta above the level of the renal arteries. The obstruction was relieved by the evacuation of clots from the aneurysm and fenestration of the internal wall. The patient died in uremia on the ninth postoperative day.

In 1955, DeBakey, Cooley and Creech [*4*] described six patients with dissecting aneurysm of the aorta treated surgically. The first patient, a fifty-eight year old man, had a dissecting aneurysm of the descending thoracic aorta of one year's duration. The patient recovered from the operation. Three months later x-ray films of the chest, including angiograms, revealed a relatively normal outline of the descending thoracic aorta. The second patient was a forty-six year old man with symptoms of six months' duration. The aneurysm involved the distal arch extending to the middle third of the descending aorta. A freeze-dried homograft was inserted but the patient died fourteen hours after the operation. The third patient was a forty year old woman with symptoms of thirteen months' duration. The aneurysm was accidentally discovered during thoracotomy for atelectasis of the left lung. The lung was found collapsed as a result of bronchial obstruction by an aneurysm of the arch of the aorta. At the initial operation pneumonectomy was performed; at the second, the aneurysm was excised and the aortic defect bridged with a freeze-dried aortic homograft. The patient recovered. The fourth patient was a man of sixty-one with symptoms of one month's duration. The aneurysm involved the distal arch of the aorta just beyond the left subclavian artery. The patient recovered. The fifth patient was a man of forty-three with symptoms of two days' duration. The aneurysm originated in the thoracic area and extended into the abdominal aorta. The patient died of a massive hemopericardium on the eighth postoperative day. The sixth patient was a seventy-two year old man with symptoms of three weeks' duration. The aneurysm involved the descending thoracic aorta. A fenestration was cut in the intima and the false passage obliterated. The patient recovered and was discharged from the hospital eighteen days later.

The most recent reported case is by Swann and Bradsher [*5*]. A forty-seven year old man was well until the day of admission to the hospital when a sharp pain suddenly developed substernally and in the neck. Later the pain shifted to the interscapular region. Nine hours after the onset of symptoms the patient underwent surgery. The operation consisted of a fenestration of the internal wall of the aneurysm to redirect the flow of blood to the normal channel. The diseased aorta was strengthened and reinforced by external wrapping with nylon cloth. The postoperative course was relatively uneventful. Six months after discharge the patient appeared well and had resumed work as an auditor.

Since submitting this article, a new report by DeBakey and co-workers [*21*] refers to a total of thirty-four cases with dissecting aneurysm of the aorta treated surgically with a mortality of 29 per cent. Hypertension was found to be highly significant in the outcome since death did not occur in ten normotensive patients (149/89 mm. Hg or less) as compared to ten deaths in twenty-four hypertensive patients (150/90 mm. Hg or more). Age did not seem to play a significant role in the mortality. In

their most recent thirty cases, the operation was performed under controlled extracorporeal circulation, with eight deaths four of which were caused by heart failure and coronary thrombosis, two by development of proximal dissection and rupture into the pericardium, one by pulmonary embolism and one by ventricular fibrillation during hypothermia.

Warren, Beckwith and Muller [*22*] reported on the surgical treatment of acute dissecting aneurysm of the aorta in five patients. One of the patients proved to have myocardial infarction with bleeding into the pericardial cavity and cardiac tamponade. One patient recovered. In their opinion, the operative risk in very early cases is outweighed by the extreme gravity of the prognosis. They advise operation as an emergency measure. Gilman and Bailey [*23*] reported a case of dissecting aneurysm of the aorta with survival in which a "double-barrelled" aorta was created. Benson, Hamilton and Claugus [*24*] reported a case treated by the fenestration procedure with fatal outcome on the ninth postoperative day. Warren, Eastwood and Muller [*25*] reported a case of acute dissecting aneurysm of the aorta with latent myasthenia gravis in whom nitrous oxide, sodium pentothal and curare anesthesia with hypothermia were used. A myasthenia crisis developed as a result of surgery and anesthesia and the patient died on the fourteenth postoperative day of tracheobronchitis and pneumonia. The postmortem examination revealed a satisfactory repair of the dissecting aneurysm.

Hirst and co-workers [*26*] made an exhaustive review of the recent English literature on dissecting aneurysm of the aorta, comprising 505 cases reported during the years 1933 to 1954. In 425 patients in whom the survival period was noted, 49 per cent died within the first four days and 91 per cent within the first six months of the onset. Most of the patients with long survival were diagnosed in retrospect, dissection being discovered at autopsy. The claims for long survival on the basis of clinical diagnosis and subsequent recovery, were less convincing.

COMMENTS

Incidence. Approximately 1 per cent of all sudden deaths, exclusive of those due to violence, are ascribed to dissecting aneurysms of the aorta [*6*]. Men are more susceptible than women, in the ratio of 2:1 or 3:1, the ages being commonly between fifty to sixty years. Schnitker and Bayer [*7*] analyzed the published reports on 580 patients of all ages and found 141 (24 per cent) of them were under forty years old. Of the 141 patients, ninety-two were males and forty-nine females. In twenty-four of the latter (49 per cent) the accident occurred as a complication of pregnancy. In addition to pregnancy, dissection of the aorta has been found in association with congenital valvular disease, hypoplasia or coarctation of the aorta and other vascular anomalies [*8,9*].

Etiology. Most investigators subscribe to the view, expressed by Erdheim [*10*], that dissection of the aorta is due to cystic necrosis of the media. However, medionecrosis is not found in all patients. As a result of necrosis of the media, a hematoma develops due to rupture of the nutrient vasa vasorum. When the hematoma develops to a certain size or with, sufficient rapidity, it ruptures through the intima at one site, occasionally several sites, producing rents through which the blood from the aorta under higher pressure enters the aneurysmal sac. From the literature Gore [*9*] collected twenty-three cases of hemorrhage occurring without intimal rupture. Spontaneous cleavage of the degenerated media may occur without hemorrhage and lead to death as a result of functional arterial obstruction indistinguishable from that resulting from other causes [*11*].

The dissection commonly begins in the ascending aorta and arch near the left subclavian artery. Rottino [*12*] noted that medial degeneration, as evident in loss of muscle cells, disintegration of elastic elements and the creation of intercellular spaces filled chiefly with basophilic mucoid fluid, is most apt to occur in this location. The hematoma spreads proximally to involve the root of the aorta, at times causing aortic insufficiency, the coronary arteries being sheared in the process. The hematoma spreads distally and may travel the entire length of the aorta shearing peripheral arteries and causing ischemia of the supplied viscera. In most patients the adventitia ruptures sooner or later, and the blood escapes into the pericardial, pleural or abdominal cavities. It is estimated that approximately 10 per cent of such patients recover.

An additional factor in the localization of the hematoma to the media is believed to lie in the structure of the aorta itself. Burman and Dieter Geratz [*11*] quote von Mölendorff to the effect that the media is composed of elastic and muscle elements which are arranged more circularly in

the inner wall and more longitudinally in the outer. Since the two layers possess different elasticity they are more apt to spread apart once cleavage begins. The element of exertion in the development of dissecting aneurysm of the aorta is minimized by most observers, although many instances are on record in which the dissection occurred after strenuous exercise or immediately after parturition [*13*]. Some workers also question the importance of hypertension and arteriosclerosis in the pathogenesis of the disease inasmuch as a sizable number of dissections occur in the young in the absence of hypertension or arteriosclerosis. It has been shown that the location of the tear in the intima bears no relation to disease of the intima but depends on underlying medial changes [*6*]. Furthermore, the normal aorta can withstand high internal pressure.

Diagnosis. In 1933 Shennan [*13*] reviewed the literature consisting of 317 cases of dissecting aneurysm of the aorta and added seventeen of his own. The diagnosis was made clinically in seven patients (2.2 per cent). In 1950 Levinson and co-workers [*14*] reviewed the recent literature, comprising 734 cases, and noted that a diagnosis had been made antemortem in eighty-eight patients (10.6 per cent). Of their own fifty-eight cases, a correct diagnosis was made in sixteen (27.5 per cent). Currently the disease is being diagnosed in approximately 50 per cent of patients. To a large extent the diagnosis depends on the basis of exclusion of other possible causes. But there are a number of features in the symptomatology and physical findings which are of particular significance. The excruciating nature of the pain in the back, at times radiating to the abdomen and extremities, is indescribable. Dyspnea, cyanosis and occasionally shock may be present. Noteworthy is the fact that blood pressure is maintained. Peripheral signs of ischemia are expressed in weakness, pain and paresthesia of the extremities or pain in the region of the kidney if the renal arteries are involved.

The physical examination may reveal a diastolic or systolic murmur over the precordium or a combination of murmurs. In our own patient the systolic murmur transmitted to the lower left part of the back was quite pronounced. Feldman [*15*] questions the significance of such murmurs because they may have been present before the occurrence of the dissection. Evidence of aortic regurgitation due to dilatation of the aortic ring is of diagnostic value. The ratio of aortic diastolic murmurs with dissection is much higher than might be expected among average hypertensive patients [*18*]. One may also elicit a systolic thrill over a peripheral vessel or in the episternal notch. Green and Saphir [*16*] draw attention to the presence of ecchymosis of the abdominal wall as a sign of dissecting aneurysm of the aorta.

The roentgenological findings are most informative, especially if the dissection develops slowly. There is progressive widening of the aortic shadow with diminished or absent pulsation in contrast to active pulsation of the involved portions. Swann and Bradsher [*5*] reported a case in which the roentgenogram of the chest revealed only slight flattening and irregularity of the aortic knob and was otherwise within normal limits. To confirm the presence of dissecting aneurysm, angiocardiography, first utilized by Golden and Weens [*17*], is invaluable especially if surgical intervention is contemplated. The dye is heavily concentrated in the normal aortic channel, the false passage being visible faintly, either laterally or medially. The combined width of both densities approximates that seen in the conventional chest roentgenogram. The electrocardiogram may be helpful in differential diagnosis if there are no changes characteristic of myocardial infarction [*18*]. The laboratory findings are non-informative. There is often leukocytosis with increased neutrophils, moderate anemia and increase in the erythrocyte sedimentation rate. Since the majority of the patients have arteriosclerosis and hypertension, abnormal laboratory findings need not necessarily reflect the presence of a dissecting aneurysm.

Mote and Carr [*6*] studied sixty patients with acute dissecting aneurysm of the aorta, examined during a five-year period at the San Francisco Coroner's Office. The various diagnoses made by physicians who attended twenty-six of these patients included three in which a correct diagnosis was made. The diagnoses in the remainder were "cardiac condition" (heart failure, myocarditis, cardiac asthma), coronary occlusion, cerebral hemorrhage, carcinoma of stomach with hemorrhage, and lumbago. It should be noted that in this group the dissection was rapidly fatal. Patients with subacute and chronic dissections are much more apt to be diagnosed correctly.

Treatment. Until a few years ago the management of dissecting aneurysm of the aorta has been expectant and symptomatic [*19*]. Thoracic

surgery has now evolved to a stage in which a direct attack on the dissection is possible in certain cases. In a recent communication, DeBakey [20] refers to ten surgically treated patients personally observed, of whom seven recovered. In essence, surgery aims at duplicating nature's way of healing the disease. A "double-barrelled" aorta is established by producing a fenestration of the intima, allowing the blood from the false channel to re-enter the main stream. The fenestration may be combined with excision of a localized segment of the aorta and reinforcement of the latter with Gelfoam or cellophane wrapping, as was used in the present instance. Occasionally, the defect requires an aortic homograft. In one of the cases reported by DeBakey and co-workers [4], a localized aneurysm was excised completely and the defect repaired by suture approximation of the lateral margins of the aortic wall. Excisional surgery is seldom feasible because the dissection is not sufficiently localized to permit such excisions.

SUMMARY

A case is described of a sixty-two year old man with antecedent hypertension, arteriosclerosis, psoriasis and psoriatic arthritis in whom a diagnosis of dissecting aneurysm of the aorta was made. This was subsequently confirmed by angiocardiography. Fenestration to the aorta was performed in which a double-barrelled channel was established to enable the blood from the aneurysm to re-enter the main stream. The patient was discharged ten days after operation in good condition. Two weeks later, because of epigastric pain, blood in the stool, and spitting of bright red blood, he was readmitted to the hospital. However his condition worsened and he died the same day. It was suspected that the cause of death was proximal extension of the dissection, possibly involving the pericardium and causing heart tamponade. Autopsy was not performed.

The available case reports on the surgical treatment of dissecting aneurysm of the aorta are reviewed.

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So-called Primary Ulcerohypertrophic Ileocecal Tuberculosis*

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Hypertrophic, tuberculous enteritis became an uncommon diagnosis after the description of regional ileitis by Crohn et al. in 1932 [*1*]. The number of reported cases of tuberculous infestation of the intestines, at least in the absence of active pulmonary disease, decreased markedly and the authenticity of nearly all of those reported earlier has been questioned unless microscopic proof was presented [*2*]. The basis for this apparent decrease in incidence is evident in Butler's [*3*] review of granulomas of the intestines at the London Hospital. During the years 1922 to 1936 operative findings suggestive of ileocecal tuberculosis were found in seventy-six patients, whereas during the period 1937 to 1952, of sixty-two patients with similar operative findings only twelve proved to have tuberculosis, while in forty the pathologic description was that of so-called Crohn's disease. As other disease processes with a similar pathologic picture have become recognized and rigid criteria for the establishment of the diagnosis of tuberculous enteritis laid down, the occurrence of ileocecal tuberculous enteritis in the absence of active pulmonary tuberculosis has become rare [*4,5*]. This is particularly true in the United States but is not so evident in other regions, such as India [*6,7*].

At the present time at least one of the following criteria is considered to be essential before a diagnosis of tuberculous enteritis may be established [*8,9*]: (1) animal inoculation or culture of suspected tissue resulting in growth of the tuberculous organism; (2) the histologic demonstration of Mycobacterium tuberculosis in the lesion; (3) the histologic evidence of tubercles with caseation necrosis; and (4) a good typical gross description of operative findings with biopsy of a mesenteric node showing histologic evidence of tuberculosis.

Based on the gross morphology of the disease process tuberculous enteritis may be divided into three types: ulcerative, hypertrophic and ulcerohypertrophic.

The ulcerative type is usually secondary to pulmonary infection, although a few primary cases have been reported [*4*]. Its incidence has ranged from 10 to 90 per cent of all patients with pulmonary tuberculosis in various x-ray and autopsy series [*10–15*]. However, since the advent of the antitubercular drugs this incidence has dropped to as low as 1 per cent [*13*].

Hypertrophic or hyperplastic tuberculosis is also known by a number of synonyms—nodular and scirrhous intestinal tuberculosis, neoplastic cecal tuberculosis, and intestinal tuberculoma. It occurs in the absence of pulmonary tuberculosis in 70 per cent of patients [*16*] and is located in the ileocecal region in 85 per cent of recorded instances [*17*].

The ulcerohypertrophic form is a combination of the two preceding types and is most frequently classified under the hypertrophic variety.

Blatin [*18*] and Duguet [*19*] are reported to have been among the first to describe the tuberculous cecal tumor. The first published report concerning surgery of intestinal tuberculomas was that of Hartman and Pilliet in 1891 [*20*]. From 1900 until Wolpaw's review of the literature in 1938 [*2*] only twenty-six cases of hyperplastic tuberculous enteritis were reported. In most of these the pathological details were so meager that the diagnoses may be questioned. Similar doubts regarding the past literature were expressed by Crohn [*5*] and Bockus [*4*] in 1940.

The differential diagnosis of hypertrophic ileocecal tuberculosis may be reduced to con-

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sideration of seven entities which ultimately require at least microscopic visualization before a definitive diagnosis is justified. These include regional ileitis (Crohn's disease) or ileocolitis, non-caseous tuberculated enterocolitis (Boeck's sarcoidosis), ameboma, actinomycosis, ulcerative colitis, non-specific granuloma and malignancy. The gross appearance of any one of these conditions may simulate any one of the others; however, most pathologists now feel that histological differentiation is quite possible [*21,22*].

ETIOLOGY AND PATHOGENESIS

In 1868 Klebs [*23*] produced enteric ulcers in guinea pigs by feeding them bovine and human tuberculous matter. Lichtheim in 1883 [*24*] demonstrated the presence of tubercle bacilli in the stools of patients with tuberculous enteritis. In 1924 [*25*] and later in 1935 [*26*] and 1944 [*27*] tubercle bacilli fed to animals under experimental conditions produced characteristic intestinal lesions. Other possible routes of infestation include the hematogenous route [*28*] and direct contiguity, as in primary tuberculosis of the female genitalia [*29*].

In 1932 [*30*] Blacklock held the bovine strain responsible in 59 per cent of the children under five years of age who were suffering from intestinal tuberculosis in Great Britain. A number of authors have believed that the tuberculoma type of lesion, occurring at any age, is more likely to be due to the bovine strain. However, in India, Ukil [*31*] and Anand [*6*] recovered the human strain in nearly all of their patients. The decreased incidence of hyperplastic tuberculous enteritis in this country has been thought to be due to the nearly complete elimination of tuberculosis from cattle, a point which favors the bovine organism as the predominant cause of intestinal tuberculomas.

Following ingestion of the organism, the acid-fast bacillus passes through the stomach, where it is protected against digestion by its fatty capsule, into the small bowel. In decreasing order of frequency the organism initiates a focus of infection in the ileum, colon, jejunum, appendix, sigmoid colon, rectum, duodenum and stomach [*32*]. Approximately 85 per cent of the lesions are located in the ileocecal region [*6,17*]. A number of factors have been considered to play a part in determining the localization of the disease: (1) areas of increased physiologic stasis, (2) regions of most abundant lymphoid tissue, (3) areas of increased rate of absorption, and (4) areas where the small bowel contents are more completely digested, thus permitting freer contact of the acid-fast bacillus with the mucous lining [*9,29*].

According to Boyd [*33*], after transport of the organism to a site of stasis the bacillus becomes localized in the depths of the glands of the mucosa and initiates an inflammatory reaction. The bacillus is carried through the epithelial layer by phagocytes to the submucosa where the initial lesions form in the lymph follicles or Peyer's patches [*34*]. The overlying mucosa, deprived of its blood supply through endarteritis, may slough, forming ulcers. The most active inflammation takes place in the submucosa. It becomes thickened as a result of edema, cell infiltrates, lymphatic hyperplasia, formation of tubercles, and fibrosis. Lateral spread and penetration through the wall to the serosa, where tubercles may be visualized on gross examination, occur via lymph channels or by direct contiguity. The mesenteric nodes are invaded through transportation of tuberculous material along lymph channels. These lymph nodes show the complete range of changes from hyperplasia to caseation and calcification [*9*]. Anand has pointed out the importance of examining the mesenteric nodes. Only 10 per cent of his series of patients showed caseation necrosis in the bowel wall, whereas caseation was present in the lymph nodes in 100 per cent of patients [*6*]. In the end stage lymphatic obstruction results and eventually the mesentery as well as the involved bowel becomes a thick, fixed, tuberculous mass [*34*].

The typical microscopic picture of tuberculous enteritis comprises epithelioid cells, lymphocyte infiltration into lymph follicles, and nodes with giant cell formation and central caseation necrosis [*33*].

COMPLICATIONS

The hypertrophic type of tuberculous enteritis runs a chronic course characterized pathologically by a recurrent process of destruction and repair, with extensive formation of fibrous tissue. As a result, progressive thickening and scarring of the bowel wall occurs, giving it a tumorous appearance [*9*].

The most common local complication is intestinal obstruction which develops in three ways: (1) encroachment of the thickened bowel wall upon the lumen because of hypertrophy and circular contraction of scar tissue; (2) extensive

intraperitoneal adhesions, which form as a result of exudation during the earlier acute phases, eventually contract, resulting in kinking or constriction of the intestine; and (3) as a result of retraction of the mesentery and shortening of the right colon in the healing phases, the mesial wall of the cecum is drawn cephalad and medially, causing a change in the angle of entrance of the terminal ileum into the cecum from 90 to nearly 180 degrees. A kink at the ileocecal junction results, with obstruction [*29,35*].

Fistulas occur in 25 per cent of patients. They may develop between loops of bowel, between bowel and female adnexal organs, and between bowel and the external surface [*9,36*]. Usually they occur as a result of secondary bacterial invasion in the areas of necrosis, causing penetrating abscesses. Other local complications include free perforation (followed by tuberculous peritonitis), intussusception and hemorrhage. All are quite rare in this form of the disease. Since the advent of antitubercular chemotherapy there have been several reports indicating an increased incidence of free perforation of the bowel during the use of these drugs [*37*].

Systemic complications are rather frequent. The most common is malnutrition [*9*]. In Banerjea's series [*7*] 91.5 per cent of the females were amenorrheic and sterile. In 5 per cent of 310 autopsies performed on patients with intestinal tuberculosis, amyloidosis of the liver was found, while in 53 per cent there was fatty infiltration of the liver [*37*].

SYMPTOMS AND SIGNS

A pathognomonic symptom or syndrome does not occur in any form of intestinal tuberculosis [*9*]. A number of reports state that there is considerable variance, percentage-wise, among those patients with pulmonary tuberculosis who have gastrointestinal symptoms suggesting tuberculous enteritis and the number which actually show the disease by x-ray examination [*38*]. Similarly, at autopsy, many instances of tuberculous enteritis are found where no suggestive symptoms were recorded prior to death [*39*].

The most frequent age period of onset is between twenty and forty years, with a slightly greater predominance in women [*29*]. The average duration of symptoms before a diagnosis is established is three years.

In most series, pain of a cramping nature located in the periumbilical region or right lower quadrant of the abdomen is both the most frequent chief complaint and frequent symptom. Weight loss is next in frequency and averages 25 pounds in one year [*29*]. While diarrhea is referred to in all articles it is surprising to note that the incidence reported is only in the range of 30 to 40 per cent [*9*]. It is usually intermittent in character, frequently occurring with exacerbations of pain, but it may be protracted and debilitating. Anorexia is frequent, but seldom has been differentiated from sitophobia. Hemorrhage is infrequent, despite the not uncommon concomitant ulceration. This is probably because of associated obliterative endarteritis. The incidence of symptoms and signs, as recorded from Hoon's [*9*] well studied series of cases of ileocecal tuberculosis, is given in Table 1.

TABLE 1
INCIDENCE OF SYMPTOMS ARISING FROM ILEOCECAL TUBERCULOSIS *

Symptoms	No. of Cases	Per cent
Gastrointestinal:		
Abdominal pain	51	87.9
Nausea	30	51.7
Vomiting	28	48.3
Anorexia	24	41.4
Diarrhea	21	36.2
Constipation	14	24.1
Alternating diarrhea and constipation	2	3.4
Gas	18	31.0
Flatulence	7	12.1
Borborygmus	10	17.2
Distention	13	22.4
Distress before meals	1	1.7
Distress after meals	24	41.4
Sour stomach	1	1.7
Hemorrhage	2	3.4
Relief obtained with bowel movement	9	15.5
Fistula	12	20.7
General:		
Loss of weight	45	77.6
Fever	22	37.9
Weakness	22	37.9
Nervousness	5	8.6
Night sweats	4	6.9

* Fifty-eight cases from Hoon et al. [*9*].

Physical examination generally reveals a malnourished, lethargic, weak person, although these findings are not as striking as in patients with secondary ulcerative tuberculous enteritis. Pulmonary signs are usually absent in the hypertrophic type. Tenderness and resistance to com-

pression are frequently present in the right lower quadrant of the abdomen. A mass is present in this region in 65 per cent of patients [*17*]. However, this is not pathognomonic and cannot be distinguished from neoplasm. Although signs and symptoms of obstruction are referred to frequently, there are no recent figures to indicate its actual incidence. Sigmoidoscopy is generally unrewarding. Complicating tuberculous anal fistulas have been mentioned frequently but their incidence is probably quite low, as indicated by Buie [*40*].

DIAGNOSIS

The greatest aid to the diagnosis of hypertrophic tuberculous enteritis is roentgenography. Although there are no pathognomonic signs, certain features are suggestive of the disease: (1) Stierlin in 1911 [*41*] first noted the value of x-ray motility studies of the bowel. His name is now associated with a roentgen configuration frequently seen in ileocecal tuberculosis. This is characterized by lack of retention of barium in the diseased segment of ileum and cecum, a column of barium remaining proximal and distal to the diseased area. Brown and Sampson [*42*] have explained the mechanism of this defect as due to retardation of barium proximal to the disease because of partial obstruction. The area occupied by the lesion fails to visualize because of its hyperirritable state; the barium passes rapidly through it to a region of normal tonus and size. Within the segment of poor visualization faintly outlined filling defects often may be seen which represent hypertrophic tissue. (2) String sign. The presence of a relatively long, thin stream of barium in the terminal ileum is most commonly seen in the extremely irritable or stenotic small bowel of ulcerative tuberculous enteritis or regional ileitis. (3) Single, filling defects in the cecum are frequently encountered in hyperplastic tuberculosis but cannot be differentiated from other granulomatous processes or malignancy. However, usually there is an associated shortening of the ascending colon which if marked may be of some help in the differentiation from neoplasm. (4) Dilatation, delay in emptying, and prominent valvulae conniventes of the small bowel are common in this form of the disease. (5) Gershon-Cohen [*43*] has emphasized the distorted appearance of the cecum as seen in barium-air contrast studies. The ileocecal valve may show a tendency to gape, due to ulceration or granulation progressing to fibrosis and resultant retraction of the valve lips. This is represented roentgenographically by a broad-based triangular appearance of the terminal inch of ileum (base toward cecum) and is known as Fleischner's sign [*44*].

Both the barium enema and the progress meal are helpful in diagnosis. The former provides the best means of studying the cecum and ileocecal valve while the latter gives valuable information through its depiction of the modifications of intestinal motility and organic defects (tumefaction and ulceration) in the terminal ileum. The changes in the terminal small bowel may help to differentiate the disease process from a neoplasm in the cecum suggested by barium enema, but such changes do not differentiate ileocecal tuberculosis from other granulomas.

Additional laboratory aides of importance center about bacteriologic studies. When x-ray findings such as those described, are present in conjunction with a suggestive history, tuberculous organisms should of course be sought by examination of the sputum, gastric aspirations and fecal smears, including cultures and animal inoculations. The presence of M. tuberculosis in the stools in the absence of pulmonary disease is suggestive of a primary tuberculous enteritis [*4*].

Hematologic or biochemical determinations have no definitive diagnostic value.

TREATMENT

Before the advent of the antitubercular drugs the diagnosis of tuberculous enteritis carried a grave prognosis [*45*]. It was difficult to place a segment of bowel at rest without resorting to a surgical procedure [*7*]. This was the reasoning behind the resections, exclusions and short-circuiting procedures. Medical therapy *per se* was non-specific and consisted of diethotherapy, heliotherapy, calcium gluconate and pneumoperitoneum.

With the introduction of antibiotic and chemotherapeutic agents and their almost miraculous effect on intestinal tuberculosis, medicinal therapy became the treatment of choice [*29*]. Discussion arose as to which type of drug, i.e., antibiotic or chemotherapeutic agent, should be used as the basis of therapy [*46,47*]. Streptomycin is a very effective agent in tuberculous enteritis, as evidenced often by rapid decrease in symptoms within a week and frequently complete clearance of abnormalities as seen on x-ray films [*48,51*], but it has more

recently been thought not too wise to use streptomycin initially as the principal drug [*46*]. The following reasons are given: (1) non-reversible toxic reactions may result; (2) after prolonged use of the drug resistant strains may arise; and most important, (3) the drug may be more effectively utilized in an acute situation or in preparation for surgery [*46,47*]. While the chemotherapeutic agents are somewhat less potent and give rise to some undesirable side effects, nevertheless over a prolonged period of time they are nearly as effective as streptomycin.

Definitive therapy for the hyperplastic form of ileocecal tuberculous enteritis has repeatedly been stated to include operation [*6,7,9,17*], even since the introduction of the antitubercular drugs. This is certainly true in the presence of complications such as obstruction, perforation, abscess, hemorrhage and fistula formation. Unfortunately the diagnosis of hyperplastic ileocecal tuberculosis cannot be made with assurance clinically in the absence of active pulmonary disease. The possibility of malignancy is ever present so that a tissue diagnosis is essential and operation is required. Under these circumstances resection of the lesion is most often performed and specific drug therapy subsequently administered.

CASE REPORT

J. H., a thirty-nine year old white man, was admitted to the Graduate Hospital of the University of Pennsylvania on November 13, 1956, with the chief complaints of cramping abdominal pain and diarrhea of eleven and four months' duration, respectively. The patient had been in excellent health until January 1956 when he first became aware of a churning, cramping periumbilical pain occurring immediately after the intake of food. The distress would persist for one to two hours and usually was associated with moderate nausea and belching. Shortly after the onset of symptoms, the patient had all of his teeth extracted because of exceedingly poor dentition and the possible relation of the diseased teeth to the abdominal discomfort. Despite these measures and the use of anticholinergic drugs the symptoms persisted and became progressively worse during the three months prior to admission. Severe pain could be avoided by quantitatively decreasing food intake. Several episodes of postprandial vomiting, usually within one hour, consisting of mixed food and bile, occurred during the month prior to admission.

A change in bowel habit began in July 1956. A watery diarrhea was characterized by the expulsion of yellow, rancid stools (one to four per day) containing mucus and gas.

A gradual 17-pound weight loss occurred over the year subsequent to the onset of symptoms. No gross gastrointestinal bleeding was ever noted and no chills or fever were recognized.

The past medical history was non-contributory except for a septic arthritis of the right knee in childhood requiring incision and drainage and resulting in ankylosis of the knee in a position of function. Appendectomy was performed at the age of twenty years.

The family history was interesting in that all eleven siblings had undergone appendectomy. One brother had undergone surgery for a peptic ulcer; one brother suffered from rheumatic heart disease; and one sister was hospitalized shortly before the patient's admission because of pulmonary tuberculosis.

Physical examination revealed a slender white man without evidence of great weight loss. The blood pressure was 120/80 mm. Hg; pulse, 88; respiration, 20; temperature, 98.6°F. The mouth was edentulous. Shotty lymph nodes were noted in the axilla, and larger nodes, 1.5 cm., were palpable in the inguinal regions. No abnormalities of the heart or lungs were detected. Palpation of the abdomen disclosed slight tenderness in the right lower quadrant overlying a firm, tender, slightly mobile, nodular mass measuring 5 by 7 by 5 cm. The liver, kidney and spleen were non-palpable. There was no evident distention, and peristalsis was hyperactive but not obstructive in type. Rectal examination revealed tenderness and a vague sensation of a mass in the right cul-de-sac. With straining, an extramucosal nodule was palpable in the midline of the cul-de-sac. The right knee was fixed in a position of 10 degrees flexion and marked atrophy of the right quadriceps was evident. Sigmoidoscopic examination beyond 6½ inches was precluded because of marked circular muscle spasm and considerable discomfort. The mucosa of the rectum showed no evidence of mucosal disease.

Hematologic, blood chemistry, urine, and stool examinations are shown in Table II. All were within normal range except for a moderate elevation of the sedimentation rate. An electrocardiogram tracing was entirely normal.

The chest roëntgenogram showed a small, 3 mm., calcific density in the right mid-lung field suggestive of a Gohn complex, but was otherwise within normal limits. (Fig. 1.) Films of the colon exposed November 11, 1956, demonstrated an irregularly contracted cecum and distorted barium-filled outline of the terminal ileum. (Fig. 2.) The barium meal study showed the esophagus, stomach and duodenum to be essentially within normal limits. As the meal was followed through the intestine it was noted that the small bowel loops were consistently displaced from the ileocecal region, presumably by a mass. (Fig. 3.) The terminal 10 inches of ileum appeared stiffened and its most distal 4 inches were slightly narrowed and separated from the cecum as by a thickened

TABLE II
LABORATORY STUDIES

Studies	Results
Hematology:	
Erythrocytes	4,800,000/cu. mm.
Hemoglobin	12.8 gm. %
Leukocytes	7300/cu. mm.
Neutrophils	80%
Lymphocytes	20%
Hematocrit	40%
Prothrombin time	92%
Wasserman test	Negative
Serum chemistries:	
Fasting glucose	101 mg. %
Urea nitrogen	11.4 mg. %
Alkaline phosphatase	3.9 Bodansky units
Bromsulfalein	4.5% in 45 minutes
Bilirubin (total)	0.2 mg. %
Lipase	0.76 units
Feces:	
Shape	Formed
Occult blood	2 plus
Neutral fats	None
Fatty acids	±
Striated muscle	±
Ova, parasites	None
Urinalysis:	
Specific gravity	1.022
Reaction	Alkaline
Albumin (qualitative)	Negative
Glucose (qualitative)	Negative
Urobilinogen	Positive 1:20
Microscopic	Negative
Fasting gastric analysis	
Free HCl	2 units
Total HCl	11 units
PPD no. 1	Negative
PPD no. 2	3 plus

NOTE: The serial sedimentation rates on: 11/13/56, 34 mm.; 12/12/56, 25 mm.; 1/9/57, 7 mm.; 5/4/57, 4 mm.; 10/31/57, 3 mm.

mesentery. The mucosal pattern of this area was destroyed; it exhibited a polypoid configuration. Similar changes were noted in the cecum. In most x-ray films there was a notable failure of barium to fill the terminal ileum and cecum adequately whereas the segments on either side were well outlined. This configuration was suggestive of Stierlin's sign as seen in ileocecal tuberculosis. (Fig. 4, left.) Approximately 2 feet from the terminal ileum, several loops of ileum seemed to be fixed in the pelvis and in one area the mucosal pattern appeared distorted, suggesting a "skip area." (Fig. 4, right.)

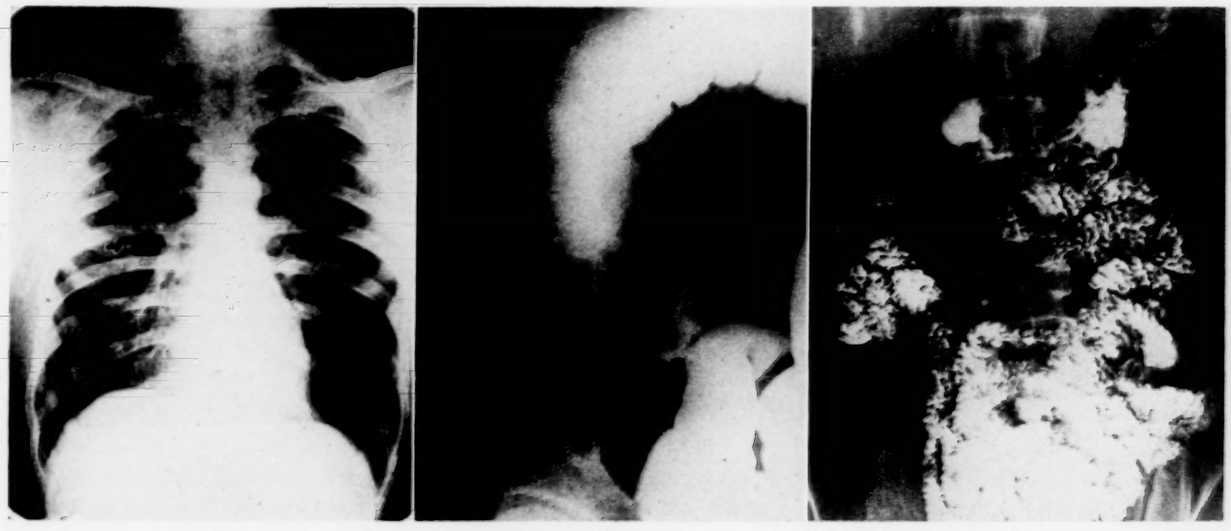
The physical examination indicated the presence of a tumor mass in the region of the cecum. X-ray film studies presented a picture compatible with a nonstenosing ileitis, but due to the character of concomitant cecal involvement and the positive Stierlin sign a granulomatous, tuberculous process was considered to be a possibility. During the fluoroscopic examination the mass was observed to move independently of the distal ileum, which suggested a third possibility of neoplasm such as lymphoma or carcinoid.

Surgical exploration on November 17, 1956, revealed the cecum and terminal 6 inches of ileum to be indurated, thickened and markedly hyperemic, and the serosal surfaces to be studded with small nodules, 1 to 2 mm. in size. In the involved area the mesenteric fat partially encroached upon the circumference of the bowel. Seven inches proximal to the ileocecal disease there was a second segment of diseased bowel, 5 inches in length, fixed in the pelvis, and similar in appearance to the ileocecal mass. The mesentery of the entire ileum was grossly thickened and succulent. Many of the mesenteric nodes measured 2 to 4 cm. in diameter, especially those along the ileocecal and right colic arteries.

The terminal 2 feet of ileum, the cecum and proximal ascending colon and as much of the involved mesentery as possible were resected and an end-to-end terminal ileo-(mid-ascending) colostomy was performed. The surgical diagnosis was regional ileitis with skip area or possible hyperplastic tuberculous enteritis.

The gross pathologic report on the resected specimen was similar to the surgical opinion except to note that the resected ileum was considerably shortened by the attached fan-shaped piece of mesentery which measured 7 cm. in thickness. The mucosa of the proximal area of involvement (so-called skip area) on close inspection revealed minute submucosal nodules 0.5 to 2.0 mm. in diameter. (Fig. 5.) The wall of the ileum was 1 cm. in thickness in the mid-portion of this lesion, in the center of which was a flat, relatively smooth area of ulceration occupying the entire 5 cm. circumference of the bowel. The most distal lesion in the terminal 17 cm. of the ileum showed several small ulcers. In this segment the wall of the bowel became 2 cm. in thickness and the total circumference was 7 cm. In the most diseased portion proximal to the cecum a large well defined oval ulceration was found measuring 6.5 by 4.5 by 0.6 cm. The ulceration continued through the valve in trough-like fashion, with scattered tufts of hyperplastic mucosa. The disease process extended into the cecum and ascending colon to about 2.5 cm. distal to the valve. All of the lymph nodes were well encapsulated and on section revealed a firm, glistening, semitranslucent white tissue without gross evidence of caseation.

Microscopic examination of tissue blocks taken from the diseased areas of the ileum showed submucosal nodules containing poorly defined epithelioid cells, one to six multinucleated giant cells and, in some



1 2 3

FIG. 1. Chest roentgenogram. Essentially within normal limits except for calcific density (arrow), 3 mm., in right mid-lung field.

FIG. 2. Barium enema. Note contracted, irregular, poorly filled cecum and distorted terminal ileum widely separated from cecum.

FIG. 3. Progress meal, small bowel at one hour. Valvulae conniventi of proximal jejunum slightly prominent; pattern otherwise normal. Arrows outline displacement of small bowel from region occupied by terminal ileum and cecum.

areas, central necrosis. Perinodular lymphocytic infiltration of tissue was quite evident. The lymphoid tissue was richest in places where Peyer's patches probably originally existed. In one section a single abscess was found consisting of masses of neutrophils and surrounded by epithelioid and giant cells. Many sections of the mesenteric lymph nodes showed tubercles and caseation necrosis. Acid-fast stains made on blocks of tissue from the bowel wall revealed acid-fast organisms with the characteristic morphology of tubercle bacilli. (Fig. 6.)

Cultures taken from tissue removed from the ileocecal valve, ileal lesions and lymph nodes all grew M. tuberculosis. Concentrated stool smears and stool cultures, however, failed to reveal any post-operative evidence of acid-fast bacilli.

Because of the suspicion of tuberculous enteritis from the gross specimen, the patient was given streptomycin, 2 gm. intramuscularly per day, to avoid the possible occurrence of a hematogenous dissemination of tuberculosis or flare up of an extra-enteric focus which occasionally occurs following operation. The postoperative course was uneventful. On the third postoperative day isoniazid, 150 mg. per day (later increased to 300 mg. per day), was started in conjunction with para-aminosalicylate, initially 4 gm. and before discharge 8 gm. per day. The streptomycin was discontinued after one week. This drug program was maintained until September 1957, when the para-aminosalicylate was stopped. Shortly thereafter a watery diarrhea of two to four stools per day with associated hypogastric cramps also ceased. The elevated erythrocyte sedimentation rate noted preoperatively returned to normal shortly after institution of drug therapy and has remained within the normal range. (Table II.) Two x-ray examina-

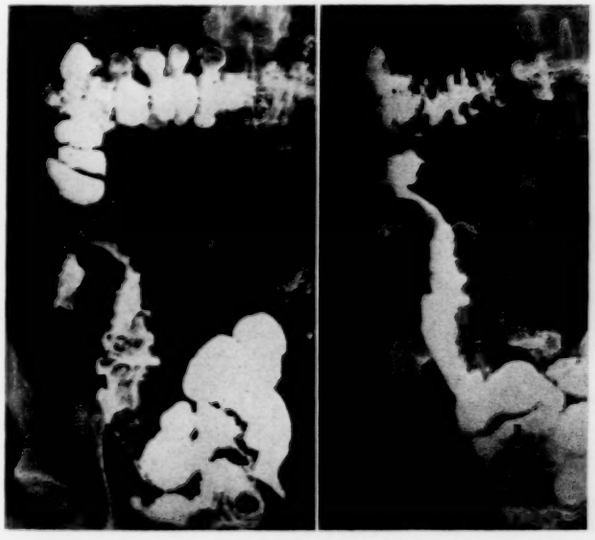


FIG. 4. Progress meal, ileocecal junction, two hours. Left, note well filled ileal loops proximal to poorly filled ileocecal area followed by normal appearing colon, suggestive of Stierlin's sign. Arrows point out filling defects in terminal ileum, suggesting polypoid or hypertrophic mucosa. Right, arrows point out possible "skip area" of disease fixed in pelvis.



5 6

FIG. 5. Mucosal surface, gross specimen, terminal ileum (to the right) and cecum and ascending colon (lower left). Arrow points out skip area. Note myriad of minute nodules over the valvulae conniventi; a large area of ulceration of most of the distal ileum and cecum, containing hypertrophic or polypoid tissue; markedly thickened, stiff wall; and fan-shaped, thick mesentery containing large lymph nodes.

FIG. 6. Photomicrograph of tubercle in the wall of the terminal ileum. Arrow points out typical acid-fast staining rod of Mycobacterium tuberculosis. Original magnification × 970.

tions of the colon by means of barium enemas on December 12, 1956, and October 31, 1957, and a progress meal study February 8, 1957, all revealed a normally functioning ileoascending colostomy with no evidence of mucosal distortion of the small bowel or colon. As of October 31, 1957, the patient had regained his pre-illness weight of 157½ pounds and was without complaint except for headaches in the morning, questionably attributed to isoniazid.

COMMENTS

The case has been presented as a rather rare example of ulcerohyperplastic ileocecal tuberculous enteritis occurring in the absence of active pulmonary tuberculosis. It is recognized that the presence of a Ghon complex may raise some doubt as to the absence of active pulmonary disease, and Kogan and Janowitz [*52*] have emphasized the point that extensive tuberculous enteritis may exist without florid pulmonary disease. However, the pulmonary lesion appeared to be completely calcified. There were no symptoms or signs suggestive of pulmonary tuberculosis during our period of observation and there was no history suggestive of active disease in the past. The ankylosing arthritis of the knee may have been tuberculous. The only known potential source of infection with which the patient had contact was with the sister who had been hospitalized for pulmonary tuberculosis.

The rare occurrence of tuberculous enteritis in the absence of active pulmonary disease is indicated by the fact that only eight reports have appeared in this country, recording a total of twenty-five cases since Crohn and Bockus' review of the literature in 1940 [*4,5,9,18,53–56*]. Seven were classified as hyperplastic, six as ulcerative in type, three were designated as examples of the ulcerohyperplastic type. Nine were unclassified. Of this entire group of reported cases there was only one (Cavin [*54*]) in which the organism was cultured and recovered following guinea pig innoculation from resected tissue and two cases (Crohn) in which the acid-fast bacillus was demonstrated histologically. A case reported by Rankine [*29*] is questioned because although a good gross surgical description was given, including gross evidence of caseation, biopsy material failed to grow the organism on culture or inoculation or show a typical tubercle with caseation microscopically. Bockus et al. [*4*] found the organism in the stools of two patients reported by them and found typical histologic evidence of tuberculous enteritis at autopsy in one patient without evident primary pulmonary involvement. Subsequent to that report the second patient, J. C., died of inanition and intestinal obstruction in December 1943. Autopsy revealed histologic findings typical of regional enteritis with no evidence of tuberculosis. While absolute proof of the previous existence of tuberculous enteritis is not possible, the disease process may actually have been initially tuberculosis. Taylor [*21*] noted that in the final stages of hypertrophic tuberculous enteritis there remained a thickened

and scarred intestinal wall, obliterated mesenteric vessels and secondarily hypertrophied lyphoid tissue, all without caseation necrosis or demonstrable tubercle bacilli. He concluded in comparing the relationship between chronic hypertrophic ileocecal tuberculosis and regional enteritis that in a certain proportion of cases of long-standing hypertrophic ileocecal tuberculosis the lesions may show no evidence of tuberculous etiology. Wig [*57*] supplied further proof of this possibility of histologic change in a two-stage operation for tuberculous enteritis in which typical histopathological changes in the resected nodes were found, and tissue culture grew M. tuberculosis following the first operation. At the second operation, after chemotherapy, the mesenteric nodes exhibited changes similar to those commonly seen in non-specific granuloma. He concluded that mistakes may occur in this way in the diagnosis of tissue examined after a course of antitubercular therapy in cases of tuberculous enteritis. Thus it is possible that the patient J. C., previously reported by Bockus, Tumen and Kornblum, was truly an example of diffuse, primary, ulcerative, tuberculous enteritis. The remainder of the twenty-five cases of so-called primary tuberculous enteritis in the literature were diagnosed on the basis of histologic finding of tubercles with caseation necrosis.

SUMMARY

A brief review of the symptomatology, roentgen features, histopathology and therapy of hypertrophic ileocecal tuberculosis is presented.

A case of ulcerohypertrophic ileocecal tuberculosis, in the absence of active pulmonary disease is reported. An excellent result followed surgical resection and subsequent antitubercular therapy.

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Demecolcine Toxicity*

*A Case Report of Severe Hematopoietic Toxicity and a Review of the Literature**

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DEMECOLCINE (desacetylmethylcolchicine; Colcemid®) has been frequently used in the management of acute gouty arthritis [*1–4*], with striking relief of symptoms in many cases. The drug usually does not induce the well known side effects of nausea, vomiting, abdominal cramps and diarrhea associated with administration of colchicine. It is, however, a potentially dangerous agent. Large doses have produced alopecia, stomatitis and leukopenia.

Our purpose is to describe a patient with gout in whom multiple manifestations of demecolcine toxicity were the result of treatment of an acute gouty episode and to comment on the profound hematopoietic toxicity. The literature on demecolcine toxicity will be reviewed.

CASE REPORT

A forty-one year old white master machinist was admitted to the Salt Lake County General Hospital September 23, 1957, with severe pain and swelling of the first left metatarsophalangeal joint.

His illness began in June 1953 with painful swelling of the left great toe which recurred approximately once each week and was relieved by 4.0 mg. of colchicine. He continued to have recurrent multiple joint involvement and developed tophi of the fingers, elbows and toes. In June 1954 probenecid therapy was started. In September 1956 administration of demecolcine to a total of 5.0 mg. per course was substituted for colchicine. This dose did not produce gastrointestinal symptoms nor did it relieve his acute gouty arthritis, and colchicine therapy was resumed. Despite probenecid therapy, the tophi enlarged and recurrently ruptured, discharging chalky urates. Repeated episodes of acute arthritis became unresponsive to administration of acetylsalicylic acid or colchicine. Steroid therapy and phenylbutazone were contraindicated (*vide infra*). Because of incapacitating gout, he was admitted to the hospital.

In 1942 a peptic ulcer perforated and required surgical closure. Because of persistent pain a subtotal gastrectomy was performed in 1949. He continued to have pain and a marginal ulcer was demonstrated. In February 1951 generalized peritonitis due to perforation of the ulcer required primary surgical repair. In March 1951 a revision of the anastomosis was performed. A "dumping syndrome" developed manifested by sweating, weakness, nausea and rapid gastrointestinal transit time. He had one episode of pneumonia in the upper lobe of the left lung in 1956. Except for mild anemia, there was no history of blood disorders. His father had kidney stones, but no clinical gout.

On physical examination, the blood pressure was 103/60 mm. Hg, the pulse 120 and regular, and the respirations were 20. The patient was a slender white man in obvious distress, protecting his left foot. His hair was blond with normal male distribution. The tongue was normal. The abdomen had multiple surgical scars. The left testis was small. There was no lymphadenopathy. Tophi were present over the right first, second, fifth, and left first proximal interphalangeal joints of the hands. There were fluctuant tophaceous cysts over the left first metatarsophalangeal joint, the right fifth metatarsophalangeal joint, and both olecranon processes. There was 2-plus pitting edema of the ankles. The remainder of the physical examination was normal.

On laboratory examination the findings were as follows: volume of packed red cells, 33 ml./100 ml.; hemoglobin, 10.4 gm. per cent; red blood cells, 3.47 million per cu. mm.; mean corpuscular volume, 96 μ^3; mean corpuscular hemoglobin, 30 $\mu\mu$g.; mean corpuscular hemoglobin concentration, 31 per cent; reticulocytes, 3.8 per cent; and platelets, 446,000 per cu. mm. The white blood cell count was 8,200 per cu. mm. with 68 per cent polymorphonuclear leuko-

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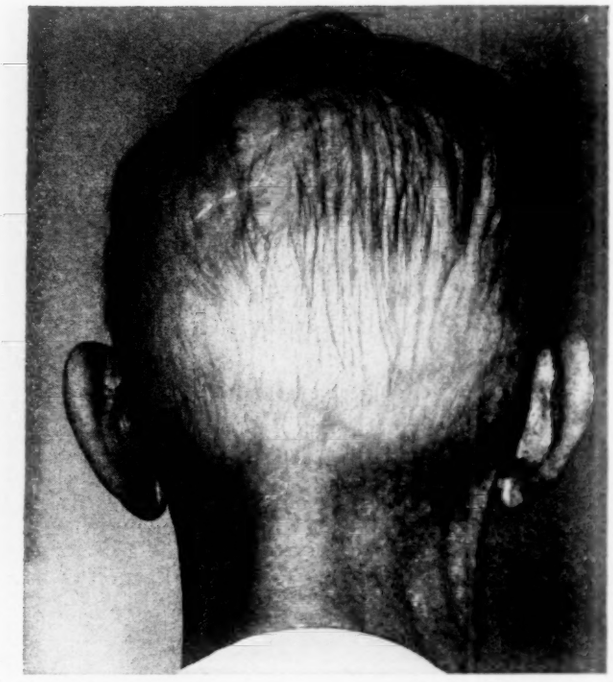


FIG. 1. Photograph of patient twenty-five days following initiation of demecolcine therapy showing marked alopecia.

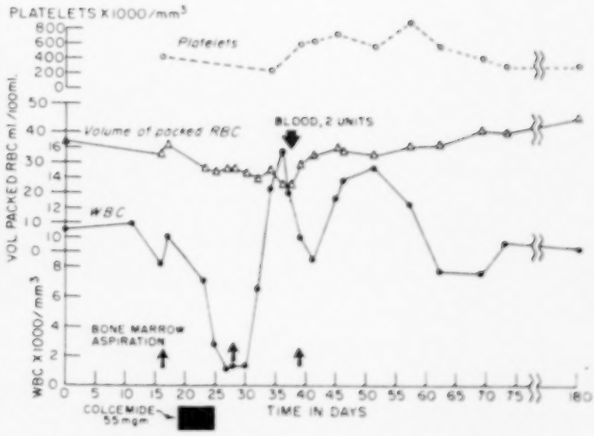


FIG. 2. The blood values illustrate the marked anemia and leukopenia resulting from demecolcine (Colcemide) administration. Bone marrow aspirations are indicated by the small arrows. The blood gradually returned to normal after demecolcine therapy was discontinued.

cytes, 2 per cent eosinophils, 23 per cent lymphocytes and 7 per cent monocytes. Except for some target cells, the red blood cells were normal.

The specific gravity of the urine was 1.005. There was no albumin or sugar. Microscopic examination revealed no abnormalities. A twelve-hour concentration test gave a specific gravity of 1.021. Phenolsulfonphthalein excretion was 15 per cent in fifteen minutes, 30 per cent in thirty minutes, and 70 per cent in two hours. Twelve stools were negative for blood (guaiac).

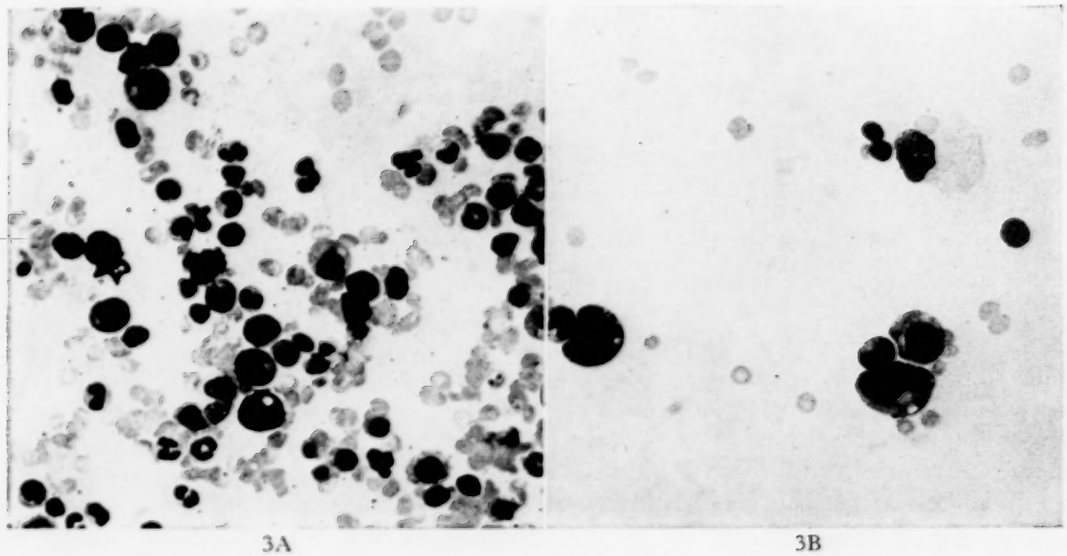
The blood urea nitrogen was 10.5 mg. per 100 ml. The serum uric acid varied from 5.6 to 10.1 mg. per 100 ml. serum. Serological test for syphilis was negative. The second strength PPD was negative. Roentgenograms showed changes of tophaceous gout.

An initial trial of colchicine, 0.6 mg. administered every hour for a total of 5.4 mg., produced nausea without relief of pain. Two days after admission the tophus over the left metatarsophalangeal joint drained spontaneously. No relief was obtained with colchicine and codeine. Base line blood counts and bone marrow aspiration were performed and demecolcine therapy was started, 1.25 mg. to be given every hour until a total of 8 mg. was administered. He was inadvertently given a total dose of 55 mg. in six days. A pararectal abscess developed four days after demecolcine was started. This was treated with sitz baths, incision and drainage. On the sixth day, he had a generalized maculopapular rash, nausea, vomiting and diarrhea. His gout was unrelieved and he was extremely ill.

Hoarseness and sore throat accompanied the institution of demecolcine therapy and persisted approximately one week after cessation of the drug. Alopecia was noted on the nineteenth day; normal hair growth returned gradually over the next three months. (Fig. 1.)

Eight days after initiating demecolcine therapy the white blood count was 1,350 cells per cu. mm. The differential count was 22 per cent juvenile neutrophils, 22 per cent segmented neutrophils, 2 per cent eosinophils, 50 per cent lymphocytes and 4 per cent monocytes. The anemia became more severe and the smear showed moderate anisocytosis and minimal poikilocytosis. The patient was given a blood transfusion on the eighteenth day. The platelet count did not change significantly, but after therapy was discontinued the platelet count rose to levels above normal. The subsequent white blood cell counts showed a sharp rise before gradually returning to normal levels. (Fig. 2.)

The bone marrow examination made before administration of demecolcine was normal. (Fig. 3A.) A second bone marrow sample taken nine days after starting therapy was markedly abnormal. This specimen was hypocellular, with a decrease in erythroid elements. (Fig. 3B.) The differential count demonstrated fewer mature granulocytes than is normal and a shift to the left as well as an increase in the plasma cells, reticulum cells and lymphocytes. The megakaryocytes were normal. These changes were consistent with a decrease of both granulocytic and erythroid elements. The M:E ratio of 5.6:1 indicated more erythroid hypoplasia than leukocytic hypoplasia. The shift of the myelocytic series to the



3A 3B

FIG. 3. Photomicrographs of the bone marrow preparations. Magnification, × 100. A, bone marrow of patient prior to demecolcine. This smear illustrates normal cellularity and cell population. B, bone marrow nine days after starting demecolcine demonstrates marked hypocellularity, absence of mature granulocytes, and absence of nucleated red blood cells. The group of three cells consists of one promyelocyte and two myelocytes which are larger than normal.

immature forms could be interpreted as a "maturation arrest" in the myelocyte stage or an increased utilization or destruction of the more mature granulocytes. For complete objectivity, the bone marrow preparations were reviewed by four other observers on a blind test, and three thought the picture was most consistent with the diagnosis of myeloblastic leukemia. The other possibilities suggested included a "myeloma-like picture" and an unusual or atypical hypoplastic anemia.

The third marrow examination following the leukocytosis showed a granulocytic response and was consistent with a return toward normal.

The patient was subsequently treated with aspirin and probenecid. Gradual improvement has taken place. Acute attacks of gout have been fairly well controlled with colchicine.

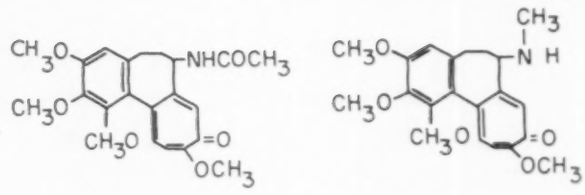
COMMENTS

Colchicum autumnale has been used since the sixth century A.D. in the treatment of gouty arthritis. The active alkaloid is present in the corm, seeds and flowers [*5*]. It has been found to have a specific action on the acute attacks of gout but is of little or no benefit in preventing tophi in chronic tophaceous gout.

The poisonous effects have been known since biblical times. These side effects, which include diarrhea, abdominal pain, nausea, vomiting, burning of the throat and skin and occasionally hematuria, have prompted a search for a less toxic agent to be used in the treatment of acute gouty arthritis.

The alkaloid colchicine was isolated from colchicum in 1820. It was found to have an effect on mitosis by Pernice in 1889 [*5*]. Further studies by Dustin [*6*], Amoroso [*7*] and Ludford [*8*] showed that colchicine acts on the cell by stimulating cell division and then interrupting mitosis at the metaphase. The antimitotic activity of cholchicine and its obvious relationship to the mitotic activity of neoplasms [*7*] stimulated an investigation of colchicine and its derivatives in cancer therapy [*9–11*].

Desacetylmethylcolchicine was isolated by Santavy and Reichstein in 1950 [*12*]. (Fig. 4.) Tissue culture studies using embryonic chick osteoblasts and tumor cells showed this new preparation to have the same antimitotic effects as colchicine. *In vitro* studies demonstrated that normal tissues were affected at about the same rate as tumors. Schär et al. [*13*] reported that the toxic effects of demecolcine were twenty to thirty times less than colchicine in a small series of animals. Moeschlin et al. [*14*] studied the effects of demecolcine in animals and in patients with leukemias and neoplasms and suggested that the depressant effect on granulocytes was quite selective. They, together with others [*15–21*], have reported satisfactory results with



COLCHICINE

DEMECOLCINE
(Desacetylmethylcolchicine)

FIG. 4. Structural formulas of colchicine and demecolcine.

TABLE 1
TOXIC MANIFESTATIONS OF DEMECOLCINE IN MAN

Hematopoietic:	Gastrointestinal:
Granulocytopenia	Stomatitis *
Lymphopenia	Nausea and vomiting *
Anemia	Diarrhea *
Thrombocytopenia	Jaundice
	Skin:
	Alopecia *
	Rash
	Pruritus
	Fever

* Most commonly noted.

continuous oral therapy of demecolcine in chronic myelocytic leukemia. However, demecolcine was less effective in other neoplasms and appeared to be contraindicated in chronic lymphocytic leukemia [*14,17*]. Demecolcine has found a place along with x-ray and Myleran® in the treatment of selected patients with chronic myelocytic leukemia.

The most hazardous untoward effect of demecolcine is related to its specific action on the granulocytes. A decrease in the number of granulocytes to dangerous levels may occur [*22–24*]. Granulocytopenia may be followed by the development of bacterial infection, and death from this cause has been reported [*24*]. Jaffe and Hyman [*22*] reported a case in which changes simulating acute leukemia occurred. Their patient was treated with 6-mercaptopurine and recovered. In retrospect they assumed that the leukemoid picture was a side effect of the demecolcine therapy and that leukemia had not developed in the patient. Thrombocytosis or normal platelet counts have been found by most authors, but thrombocytopenia has been reported [*23*]. Changes in the erythrocytes have not been described.

Paralleling the use of demecolcine in chronic myelocytic leukemia were studies of its effect in acute gouty arthritis. Favorable results in the treatment of acute attacks have been reported [*1–4,26*] and maintenance therapy has been recommended [*4*]. The response has been as dramatic as with colchicine. Doses of 4 to 10 mg. have produced good to excellent results. There is no evidence that there is a uricosuric effect. The consensus is that demecolcine is less toxic and yet as effective as colchicine in these cases.

The gastrointestinal toxicity of demecolcine is less than that of colchicine [*2–4,14,17,22,27*] but diarrhea and nausea have occurred [*1,2,4,13,14, 19,28,29*]. The initial work of Moeschlin indicated few ill effects. Subsequently, fever, rash, pruritus and other toxic manifestations have been encountered. (Table 1.)

One of the most distressing symptoms of demecolcine toxicity is an ulcerative stomatitis with large painful ulcers in the gingivae, buccal mucosa, hard and soft palate, and tongue [*2,15,17,20,28,30*]. These lesions have cleared on stopping the drug, and may not recur, even when demecolcine is administered again. Alopecia has been described. It occurs from ten days to four months after the initiation of therapy and is apparently unrelated to the dose of demecolcine. The alopecia may be partial or complete. There has been prompt and complete regrowth of hair after the drug has been stopped. In those patients whose clinical condition required maintenance therapy, regrowth has also occurred.

CONCLUSION

Demecolcine therapy for acute gouty arthritis may produce a dramatic response with relief of pain in the joints and swelling, and without the distressing gastrointestinal side effects so commonly seen with colchicine therapy. However, this very lack of gastrointestinal discomfort may inadvertently encourage increased dosage which may result in more serious toxic effects. As demonstrated by our patient, as well as those of Colsky et al. [*26*] and Jaffe and Hyman [*22*], it is possible to give much larger doses without (1) relief of gouty symptoms, (2) nausea, vomiting, or diarrhea, or (3) other signs of minor toxicity.

In our patient striking hematopoietic changes developed. The anemia and leukopenia, together with the immaturity of the granulocytic

series and increased number of cells in mitosis in the bone marrow, is not a surprising effect. Since mitotic activity occurs through the myeloblast phase and inhibition of mitosis at this point in cell development has been produced by colchicine and its derivatives [*31,32*], it seems quite reasonable to expect that demecolcine may produce so-called maturation arrest and result in an absence of mature cells, with a "shift to the left."

In chronic myelocytic leukemia, in which the ultimate outlook is of course far more grave than that of gout, the results justify the risk of using demecolcine, and indeed certain patients who are unresponsive to x-ray and Myleran may improve markedly with demecolcine therapy. In the management of gout, however, demecolcine must be considered a dangerous if sometimes useful remedy. Patients should be advised that this drug is not the same as colchicine, and that it can cause serious side effects.

SUMMARY

1. A patient with acute gouty arthritis, in whom multiple toxic effects resulted from demecolcine treatment, is described.

2. Toxic manifestations of demecolcine therapy are reviewed, with specific reference to the hematopoietic system.

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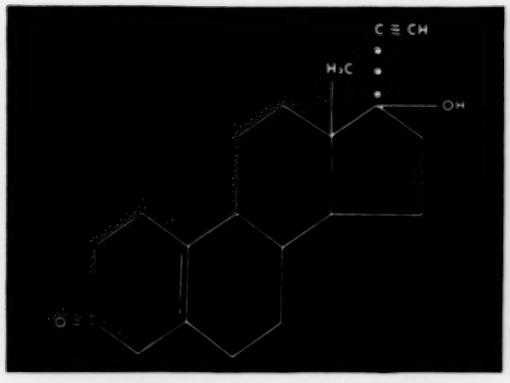
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Enovid represents a positive advance in the treatment of threatened or habitual abortion[4] and in the treatment and control of endometriosis[5]. Physicians may prescribe Enovid confidently without producing androgenic manifestations.

DOSAGE OF ENOVID FOR THREATENED ABORTION
Two or three tablets daily on appearance of symptoms. This dosage may be reduced to one or two tablets daily when symptoms disappear. The reduced dosage should be continued to term and increased if symptoms reappear.

DOSAGE OF ENOVID IN HABITUAL ABORTION
Two tablets daily as soon as pregnancy is diagnosed and continued without interruption at least through the fifth month. Enovid may be safely continued to term if desired.

DOSAGE OF ENOVID FOR ENDOMETRIOSIS
The daily dose for the first two weeks is one tablet, two tablets daily for the next two weeks, then three tablets daily for the following two weeks and finally four tablets daily for three to nine months.

G. D. Searle & Co., Chicago 80, Illinois, Research in the Service of Medicine.

1. Symposium on New Steroid Compounds with Progestational Activity, Ann. New York Acad. Sc. 71:483-805 (July 30) 1958.
2. Edgren, R. A.: The Uterine Growth-Stimulating Activities of 17α-Ethynyl-17-Hydroxy-5(10)-Estren-3-One (Norethynodrel) and 17α-Ethynyl-19-Nortestosterone, Endocrinology 62:689 (May) 1958.
3. Rakoff, A. E.: Pages 800-805 of reference 1.
4. Tyler, E. T., and Olson, H. J.: Pages 704-709 of reference 1.
5. Kistner, R. W., Endometriosis, in Conn, H. F. (editor): Current Therapy — 1959, Philadelphia, W. B. Saunders Company, 1959, pp. 610-612.

SPONTIN®

(Ristocetin, Abbott)

A STATISTICAL REVIEW* OF THREE HUNDRED THIRTY-THREE CASES

**Records of Medical Department, Abbott Laboratories, North Chicago, Illinois*

SPONTIN (Ristocetin, Abbott) is a new antibiotic discovered and developed at Abbott Laboratories. Its two components, and B, have been isola line state from the fer of a new species of *Nocardia lurida*. Bot are active against gra teria and mycobacte mycete was isolated f ple collected from th Gods, Colorado Sp No other culture wh same antibiotic has

The chemical cha ristocetins are not c though they are kn teric substances con phenolic groups a ristocetin A and ris molecules with m the vicinity of 4000 have good stability pH range of bloo SPONTIN is a ly tion, derived fr material, represe ristocetins A a

Antimicrobial tion against gra ganisms, SPON effective than able antibiotics

Against pne cocci (except s cocci) the anti tericidal at th concentration hibits the gro also kills the

This obse for the majo lococci. Ho staphylococ have been t centration s minimum i produce a this reaso SPONTIN i for the treatment and enterococcal infections.

Cultures of staphylococcus aureus, which are resistant to other antibiotics have been shown to be sensitive to SPONTIN. There has been no case reported in which a staphylococcal or enterococcal strain has exhibited a

SPONTIN

have good stability pH range of blood and tissue

SPONTIN is a lyophilized preparation, derived from pure crystalline material, representing a mixture of ristocetins A and B.

Antimicrobial Properties. In its action against gram-positive coccal or ganisms SPONTIN is notably more tly avail-

d strepto- of entero- riably bac- osage. The which in- organisms

holds true s of staphy- strains of ococci which quired a con- gher than the centration to effect. It is for her dosage of recommended staphylococcal tions.

coccus aureus, other antibi- to be sensitive as been no case taphylococcal or has exhibited a SPONTIN.

that the antibi- TIN is enhanced gamma globulin. supported by the *vivo* activity of mes greater than from the *in vitro*

estigators* have re- cal response follow- ration of SPONTIN dies have shown a vity on the part of ganism. Satisfactory may be expected sm requires up to 25 ONTIN for inhibition llowing table shows nsitivities of different he major pathogenic groups.

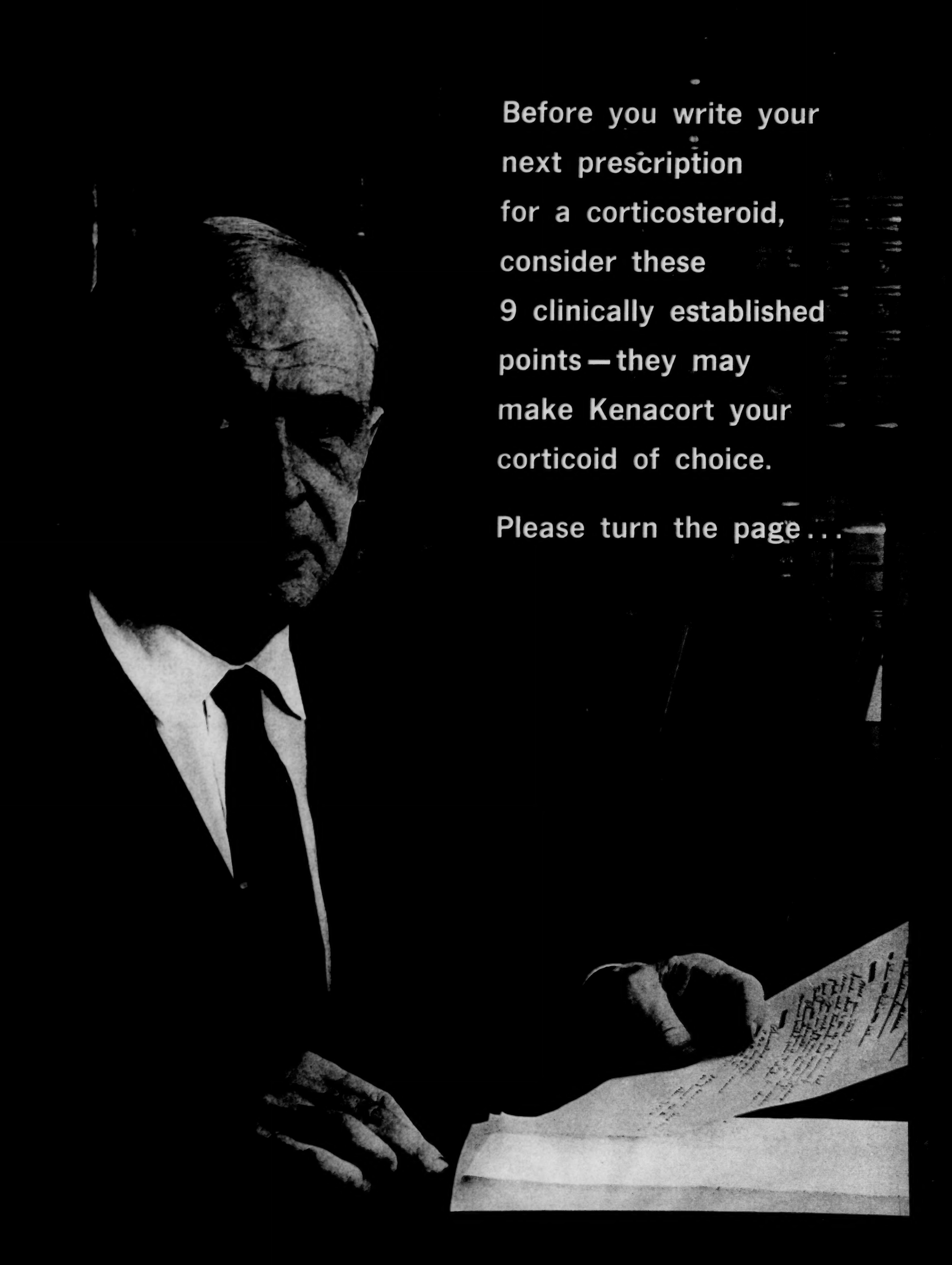
Summary and Conclusions

Major use has been treating staphylococcic infections. Of the total 333 cases, approximately one-third was treated for pneumonia; of these over 80% were either cured or improved. About 70% of these pneumonias were caused by staphylococci.

The next largest group included 46 patients with subacute bacterial endocarditis. About 50% of these infections were identified as staphylococcic and a further 15% as enterococcic. Other infections included 38 cases of septicemia, 32 abscesses and 24 patients with osteomyelitis.

The administration of SPONTIN brought about a cure in 60% of all the cases reviewed and improvement in a further 17%.

Side-effects were seldom troublesome when a daily dose of 2 Gm. was not exceeded. The incidence rose as the dosage was increased. The most disturbing side-effect after administration of SPONTIN has been neutropenia. However, in all instances this has responded to either discontinuance of medication or reduction in dose.


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initial therapy—remarkably free from complications

Allison, J. R., Sr., and Allison, J. R., Jr.:
Monographs on Therapy 3:99 (Oct.) 1958.

pre-prescription
point number **2**

continuing therapy—maintenance doses are low

Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.:
J. A. M. A. 167:58 (May 3) 1958.

pre-prescription
point number **3**

no sodium or water retention—low salt diet not necessary

Hartung, E. F.:
J. A. M. A. 167:973 (June 21) 1958.

pre-prescription
point number **4**

absence of edema

Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription
point number **5**

less likely to create electrolyte disturbance

Bongiovanni, A. M.; Mellman, W. J., and Eberlein, W. R.,
J. Pediat. 53:3 (July) 1958.

pre-prescription
point number **6**

no secondary hypertension—no significant change in pulse, respiration, or blood pressure

Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:
J. A. M. A. 167:959 (June 21) 1958.
Bernsten, C. A., Jr., and others:
New York Rheumatism Association, Annual Meeting,
New York, April 9, 1959.

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no excessive appetite

Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

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point number **8**

without unnatural psychic stimulation --does not stimulate and rarely depresses the mood

Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:
J. A. M. A. 167:959 (June 21) 1958.
Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription
point number **9**

gastrointestinal complaints infrequent

Hartung, E. F.:
J. A. M. A. 167:973 (June 21) 1958.

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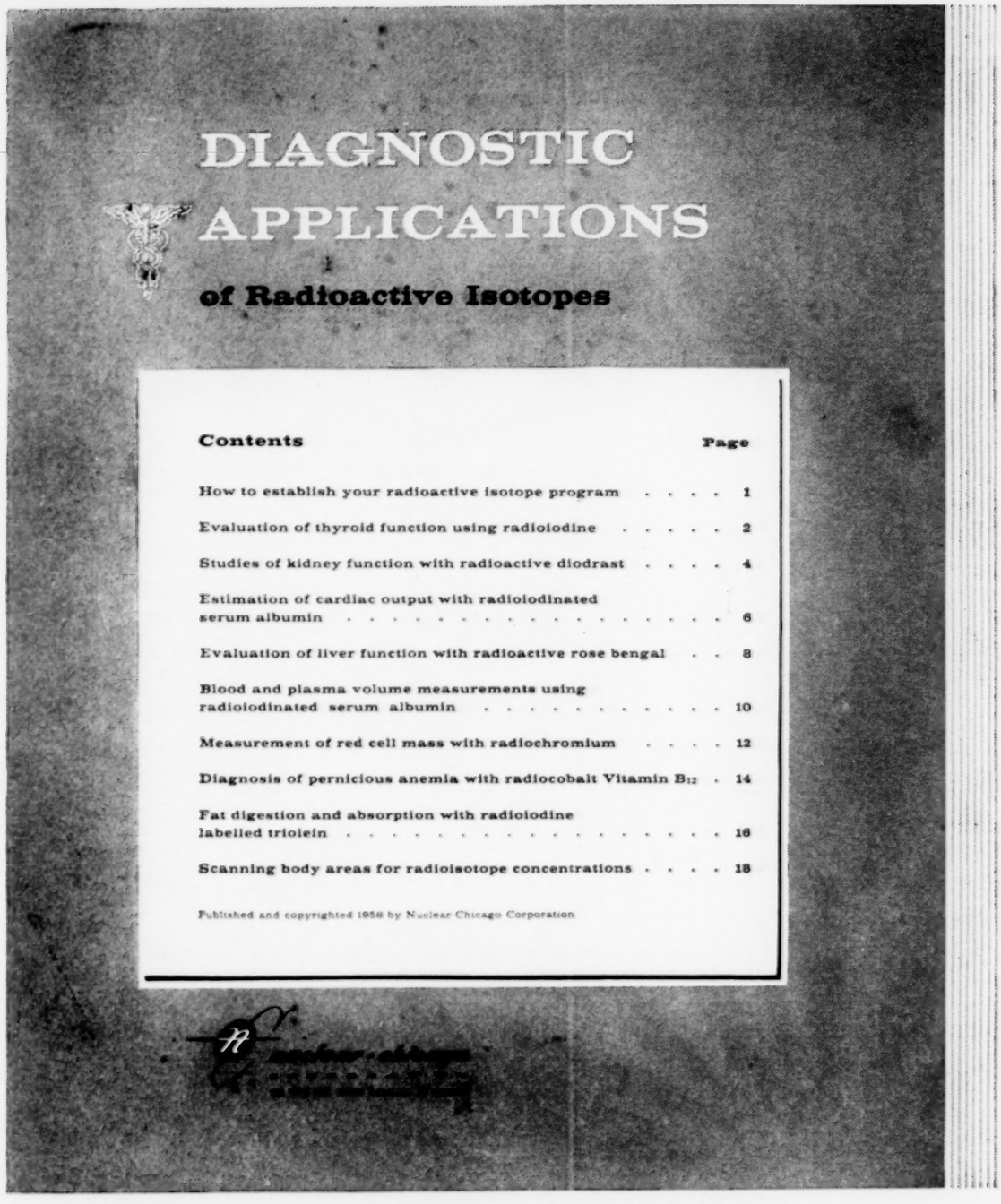
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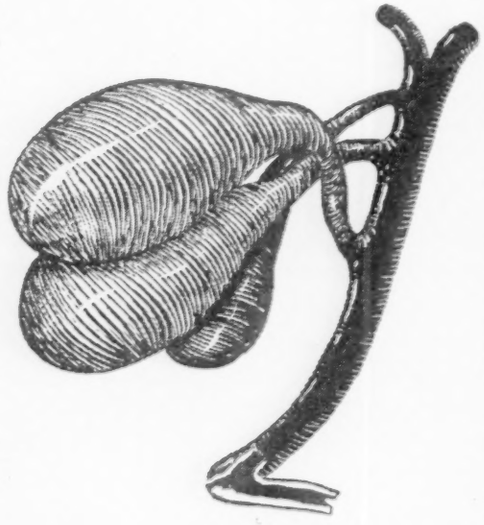
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Source: Skilboe, B.: Am. J. Clin. Path. *30*:252, 1958.



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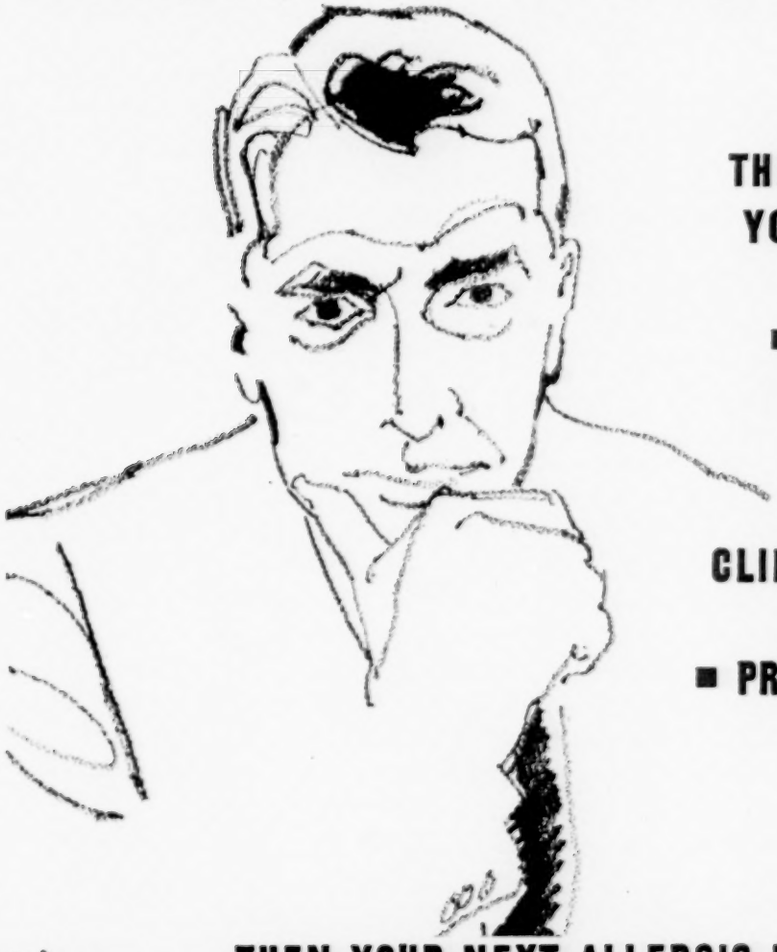
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(1) Beckman, H.: Drugs: Their Nature, Action and Use, Philadelphia, W. B. Saunders Company, 1958, p. 425.
(2) Biliary Tract Diseases, M. Times *85*:1081, 1957.

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1. Committee on New and Unused Therapeutics, Am. Coll. Allergists: Ann. Allergy **16**:237 (May-June) 1958. 2. Spielman, A. D.: Ann. Allergy **16**:242 (May-June) 1958. 3. Spielman, A. D.: New York J. Med. **57**:3329 (Oct. 15) 1957.

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A RATIONALE FOR THERAPEUTIC VITAMIN-MINERAL

Subclinical vitamin-mineral deficiency in chronic degenerative disease

Most degenerative disease changes appear to be related to disturbances of cellular nutrition.[1] Subclinical vitamin or mineral deficiencies often occur despite an adequate caloric intake, and the consequent impairment of enzyme systems may injure body tissues.[2] Considerable evidence indicates that the vitamin reserve is frequently lowered to a serious degree in the older age groups most susceptible to degenerative disorders.[3] Older persons also have increased requirements for such minerals as iron, iodine, copper, calcium and zinc.[4,5,6]



the importance of vitamins and minerals in Diabetes mellitus

The diabetic has a higher requirement for the vitamin B-complex (especially nicotinic acid, thiamine, B_{12}, and riboflavin) than the normal individual.[7] Great losses of calcium and potassium may occur during ketosis.[7] Low tissue zinc levels have recently been reported in a series of diabetic patients.[8] Metabolic deficiencies are frequently aggravated by diets which restrict or eliminate foods rich in essential co-factors.[9] Administration of more than normal requirements often produces a decided clinical improvement and may help to prevent neuropathic changes.[7]



the importance of vitamins and minerals in Digestive disorders

Peptic ulcer diets are often deficient in essential vitamins. Symptoms attributable to B-vitamin deficiency are commonly observed in patients on such diets.[10]

Liver damage leads to faulty vitamin metabolism, and cirrhosis often produces severe vitamin deficiency.[11,12] Pollack and Halpern recommend daily administration of therapeutic vitamins to patients with hepatitis or cirrhosis.[11] Large amounts of zinc are also lost by the cirrhotic patient.[13]

Great care must be exercised to avoid excessive depletion of vitamins and minerals in ulcerative colitis, regional enteritis, and chronic diarrhea. Patients with extensive bowel resections may require up to six times the normal daily vitamin requirement.[14]



the importance of vitamins and minerals in Arthritic disorders

According to Spies,[15] nutritive failure is especially frequent in arthritic or rheumatic disorders. Some patients lose the desire to eat; some are too disabled to earn money to purchase required foods; still others are unable to perform all the necessary masticatory motions. Nausea and vomiting may prevent adequate absorption.

Therapeutic vitamins prevent or correct vitamin deficiency in the arthritic on an inadequate diet. In degenerative joint disease, vitamin therapy is recommended even when there is no demonstrable deficiency.[16] Mineral supplementation may help prevent the depletion of calcium and potassium that occurs during therapy with cer-

SUPPLEMENTATION

tain of the adrenal steroids. Iron[17] may be useful in preventing the anemia common in arthritis.



the importance of vitamins and minerals in Other degenerative processes

Vitamins and minerals appear to play a role in many other degenerative processes associated with aging. Studies by Wexberg,[18] Jolliffe[19] and others indicate that many of the symptoms attributed to senility or cerebral arteriosclerosis respond with remarkable speed to the administration of vitamins. Pyridoxine and nicotinic acid may even play an important role in the prevention of atherosclerosis.

Vitamin or mineral deficiency may be an unrecognized factor in still other situations. As Kampmeier states:

"Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease. Are there 'subclinical' degrees of vitamin deficiencies to search for, now that frank deficiency states have become so rare at least in the United States?"[2]

References: 1. Kountz, W. B.: *Mod. Med.* 25:102, Aug. 1, 1957. 2. Kampmeier, R. H.: *Am. J. Med.* 25:662, Nov. 1958. 3. Overholser, W. and Fong, T. C. C. in Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 264. 4. Kountz, W. B.: *Indust. Med.* 27:537, Oct. 1958. 5. Kountz, W. B. in Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 252. 6. Carlson, A. J. in Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 80. 7. Duncan, G. G.: Diseases of Metabolism, 4th edition, W. B. Saunders, Philadelphia, 1959, p. 812. 8. Griffith, G. and Hegde, B.: *Illinois M. J.* 115:12, Jan. 1959. 9. Pollack, H.: *Am. J. Med.* 25:708, Nov. 1958. 10. Sebrell, W. H.: *Am. J. Med.* 25:673, Nov. 1958. 11. Pollack, H. and Halpern, S. L.: Therapeutic Nutrition, National Academy of Sciences and National Research Council, Washington, D.C., 1952, p. 57. 12. Kark, R. M. in Wohl, M. G. and Goodhart, R. S.: Modern Nutrition in Health and Disease, Lea and Febiger, Philadelphia, p. 615. 13. Vallee, B. L. in Harrison, T. R.: Principles of Internal Medicine, 3rd edition, McGraw-Hill, New York, 1958, p. 474. 14. Warthin, T. A. and Monroe, K. E.: *M. Clin. North America* Sept. 1958, p. 1419. 15. Spies, T. D.: *J.A.M.A.* 167:675, June 7, 1958. 16. Solomon, W. M. in Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 627. 17. Ausman, D. C.: *Journal Lancet* 76:290, Oct. 1956. 18. Wexberg, E.: *Am. J. Psychiat.* 97:1406, 1941. 19. Jolliffe, N.: *J.A.M.A.* 117:1496, 1941.

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Pyridoxine Hydrochloride	5 mg.
Calcium Pantothenate	20 mg.
Vitamin B_{12} Activity Concentrate	5 mcg.
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Vitamin E	5 Int. units
Calcium	105 mg.
Iodine	0.15 mg.
Iron	15 mg.
Potassium	5 mg.
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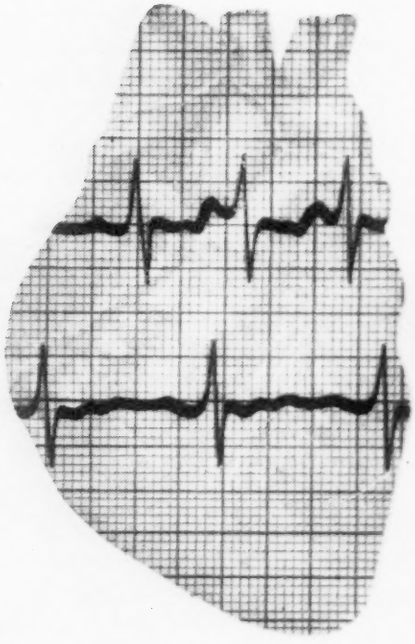
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1. Smith, J. M.: Lederle Bull. Symposium Report, 1:1, 1958.
2. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

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References:

1. Alexander, L.: J.A.M.A. 166:1019, March 1, 1958.
2. Current personal communications; in the files of Wallace Laboratories.
3. Pennington, V.M.: Am. J. Psychiat. 115:250, Sept. 1958.

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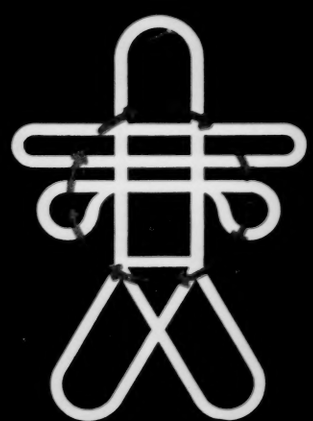
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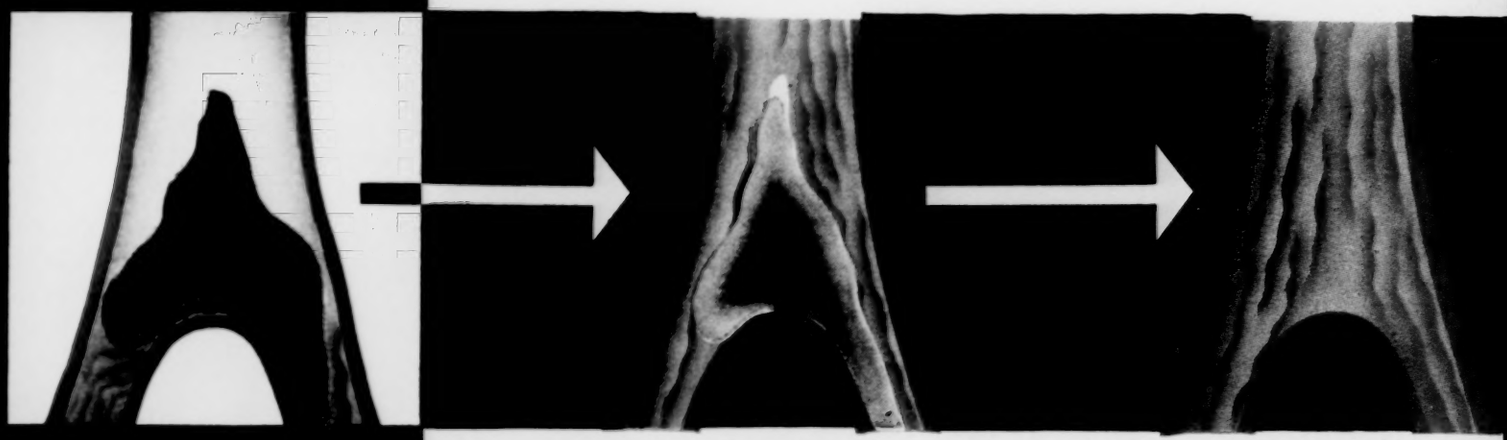
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CLOTS in thrombophlebitis and pulmonary embolism

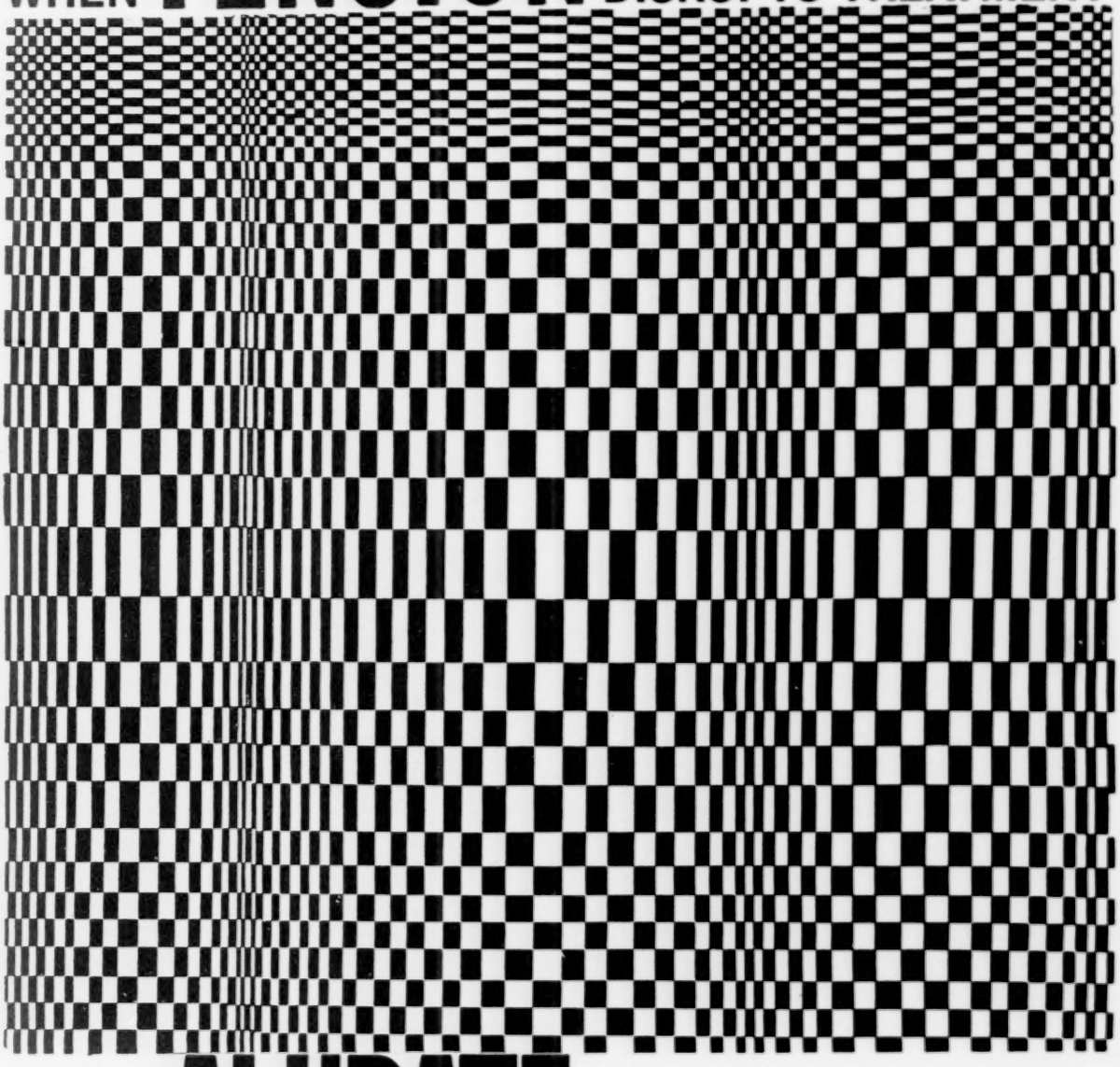


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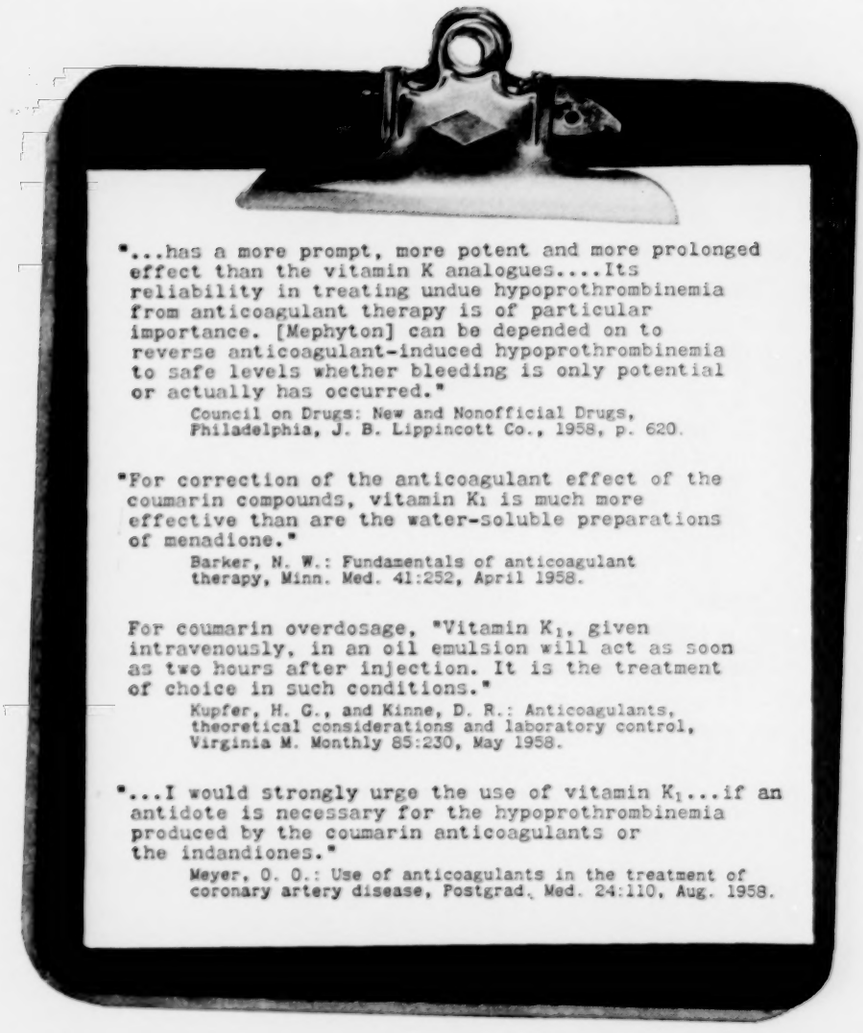
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brand of imipramine HCl

The Dawn of a New Era in the Treatment of Depression

An entirely new compound originated in Geigy research laboratories, Tofrānil:

Exercises selective action on the symptoms of uncomplicated depression

Is effective in 70-85% of cases, particularly those of endogenous depression

Is frequently successful in even the most profound and chronic cases

Is virtually devoid of serious side reactions

Reduces the need for electro-convulsive therapy

May be administered by either oral or intramuscular routes

Indications for Tofrānil include:

Endogenous Depression, Reactive Depression, Involutional Melancholia, Senile Depression, Depression associated with other Psychiatric Disorders

Detailed literature on request

Availability:

Tofrānil® (brand of imipramine HCl): Sugar-coated, coral-colored tablets, 25 mg. each, in bottles of 100. Ampuls for intramuscular administration only, each containing 25 mg. in 2 cc. of solution (1.25 per cent) in cartons of 10 and 50.

Selected Bibliography:

1. Ayd, F. J., Jr.: Bulletin of School of Medicine, University of Maryland 44:29, 1959. 2. Azima, H.: Canad. M.A.J. 80:535, 1959. 3. Azima, H., and Vispo, R. H.: Am. J. Psychiat. 115:459, 1958. 4. Kuhn, R.: Am. J. Psychiat. 115:459, 1958. 5. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. 3:155, 1958. 6. Mann, A. M., and MacPherson, A. S.: Canad. Psychiat. A. J. 4:38, 1959. 7. Sloane, R. B.; Habib, A., and Batt, U. E.: Canad. M.A.J. 80:540, 1959. 8. Straker, M.: Canad. M.A.J. 80:546, 1959.

Geigy, Ardsley, New York

05659 B

potent
and unique thymoleptic agent

Geigy

NOW

. . . a new way to relieve pain and stiffness in muscles and joints

INDICATED IN:

- MUSCLE STIFFNESS
- LUMBOSACRAL STRAIN
- SACROILIAC STRAIN
- WHIPLASH INJURY
- BURSITIS
- SPRAINS
- TENOSYNOVITIS
- FIBROSITIS
- FIBROMYOSITIS
- LOW BACK PAIN
- DISC SYNDROME
- SPRAINED BACK
- "TIGHT NECK"
- TRAUMATIC STRAINS AND BRUISES
- POSTOPERATIVE MYALGIA



■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain

■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids

■ More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with any previously used analgesic, sedative or relaxant drug.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets.

Literature and samples on request.

WALLACE LABORATORIES, NEW BRUNSWICK, N. J.

New Enzyme-controlled antifungal therapy to meet the growing challenge of Monilial Vaginitis

IN PREGNANCY / IN DIABETES / AFTER ANTIBIOTIC THERAPY–Today, monilial vaginitis is estimated to be a problem in at least 33 per cent of pregnant women and about 10 per cent of nonpregnant females[1]—a rapidly increasing incidence attributed partly to the widespread use of antibiotics.

"Vanay" Vaginal Cream broadens the scope of specific therapy: (1) "Vanay" insures a continuous therapeutic fungistatic effect without danger of local reaction; (2) in addition, "Vanay" restores and maintains a physiologic pH and normal vaginal flora—reducing risk of reinfection.

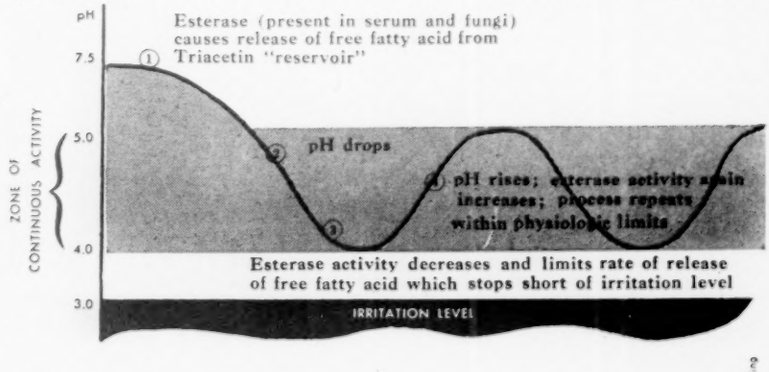
Effective response: Treatment was notably effective in moniliasis, as confirmed by symptomatic relief and post-treatment smears, Assali reports.[2] Marked clinical improvement was also noted in 154 of 206 patients, and in some cases symptoms subsided within a week of therapy.[3]

Other advantages: No monilial resistance demonstrated[4] / prolonged duration of activity[4] / nonsensitizing / nonirritating / nonstaining / odorless.

"VANAY" Vaginal Cream

BRAND OF TRIACETIN IN NONLIQUEFYING BASE

UNIQUE ENZYME-CONTROLLED FUNGISTASIS WITHOUT IRRITATION



Indications: specific in monilial vaginitis...adjunctive in trichomoniasis . . . also valuable in nonspecific vaginitis where an acid pH must be restored and maintained.

Usual Dosage: 2 to 4 grams daily.

Supplied: No. 204-250 mg. Glyceryl triacetate per gram in a nonliquefying base. Combination package: 1½ oz. tube with 15 disposable applicators.

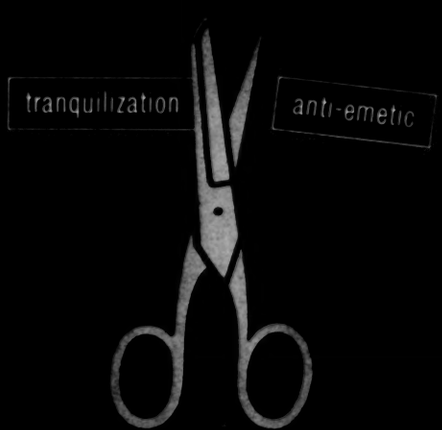
References: 1. Idson, B.: Drug & Cosmetic Industry *84*:30 (Jan.) 1959. 2. Assali, N. S.: Personal communication. 3. Combined results of 18 clinical investigators, Medical Records, Ayerst Laboratories. 4. Kubista, R. A., and Derse, P. H.: Antibiotics & Chemotherapy, to be published. 5. Knight, S. G.: J. Invest. Dermat. *28*:363 (May) 1957. 6. Knight, S. G.: Antibiotics & Chemotherapy 7:172 (Apr.) 1957.

Ayerst

AYERST LABORATORIES
New York 16, N.Y. · Montreal, Canada
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LICENSED BY WISCONSIN ALUMNI RESEARCH FOUNDATION

Patent Applications Pending



MELLARIL is virtually free
of such toxic effects as
· jaundice
· Parkinsonism
· blood dyscrasia

SANDOZ

Mellaril®

remarkable lack of side effects

In more than 3,000 carefully-followed patients, Mellaril has been almost completely free of such major side effects as jaundice, extrapyramidal symptoms, Parkinsonism, blood dyscrasia, dermatitis—even when given in quantities far in excess of the usual dosage.

"POVERTY" OF SIDE EFFECTS

"The most striking aspect of thioridazine [Mellaril] therapy is the poverty of side effects.... In its lack of side effects and low toxicity, it is superior to all other tranquilizing drugs tested. For this reason also it is well tolerated by patients, particularly those who are not hospitalized and who frequently discontinue their medication because of dizziness, sleepiness, increased tension or parkinsonism with other drugs."[2]

NEGLIGIBLE SIDE EFFECTS

"Side effects were negligible at all dosage levels: no incidence of parkinsonism or other extrapyramidal symptoms. Minimal sedation, on the whole lower than with other tranquilizing agents. No alteration in liver function, urine or blood. No photosensitivity. Patient acceptability was exceptional: lack of drowsiness, lethargy or 'washed out' feeling, permitted patients to carry on normal everyday activities. Orthostatic hypotension was absent. The initial 'keyed up' tense feeling common to other drugs of this type was absent.... Patients forced to interrupt treatment with other phenothiazine derivatives because of parkinsonism or other extrapyramidal symptoms were able to continue therapy with thioridazine without appearance of parkinsonism."[3]

SINGULARLY FREE OF SIDE EFFECTS

"The extrapyramidal syndrome was not encountered in any of its forms. Dizziness and sleepiness responded to a reduction in dosage. Other side effects did not occur.... It is singularly free from the side effects ordinarily seen with these [phenothiazine] compounds."[4]

ABSENCE OF SIGNIFICANT SIDE EFFECTS

"None of the following toxic effects, so common after administration of the phenothiazines, was present during the period of Thioridazine administration: Parkinsonism or Parkinson-like symptoms, photosensitivity, orthostatic hypotension, bone-marrow depression."[1]

MINIMAL SIDE EFFECTS

"Side effects such as extrapyramidal activity, jaundice and photosensitivity have not been observed in patients treated with Thioridazine [Mellaril]. Extrapyramidal side effects produced by other phenothiazines have disappeared promptly with no deterioration in the behavioral response when these patients have been shifted to Thioridazine."[5]

NO JAUNDICE

"No allergic reactions were observed such as skin eruptions, jaundice or agranulocytosis. Central nervous system toxicity, as manifested by extrapyramidal effects, seizures, and excitement did not occur despite the use of high doses (up to 2000 mg.) of the drug."[6]



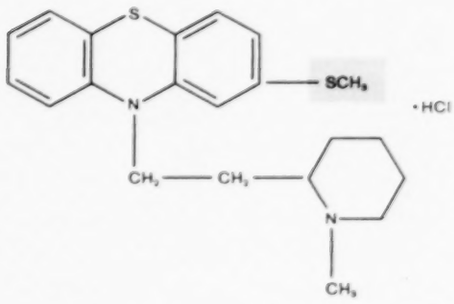
Mellaril®

THIORIDAZINE HCl

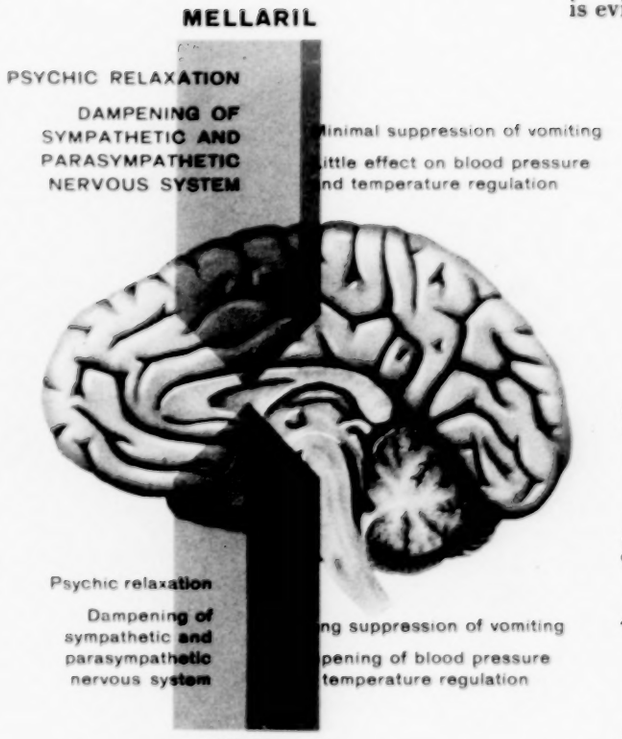
specific, effective tranquilizer • safer at all dosage levels



a new advance in tranquilization:
greater specificity of tranquilizing action plus fewer side effects



1 A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.





2 Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.

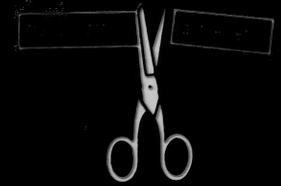
3 A notable absence of extrapyramidal stimulation.

4 Lack of impairment of patient's normal drive and energy, while achieving psychomotor control in mental and emotional disorders.

5 Virtual freedom from toxic effects — jaundice, photosensitivity, skin eruptions, disturbed body temperature regulation, blood forming disorders have been absent in reports currently available.

These properties add up to a greater margin of safety in general office practice, in ambulatory psychiatric out-patient clinics, and in hospitalized patients.

Mellaril®



excellent clinical response

In office practice and in hospitalized patients, Mellaril has proved highly useful for a wide variety of major and minor emotional disorders (such as anxiety, tension, apprehension, alcoholism, agitated psychoneurosis, agitated psychotic states, etc.).

EXTREMELY SATISFACTORY ". . . produced extremely satisfactory results in the broad therapeutic range represented in this series."[3]

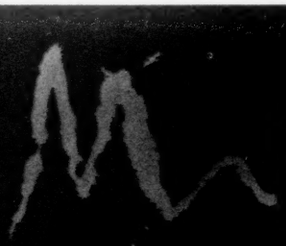
POTENT AGENT ". . . appears to be a potent agent in the symptomatic management of a variety of psychiatric states."[4]

MAJOR ADDITION TO THERAPEUTICS "This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."[1]

AN ACTIVE AGENT "Thioridazine is an active therapeutic agent. . . . It is effective in a variety of psychiatric disorders, including schizophrenic reactions. . . . The drug is particularly advantageous for a group of schizophrenic patients who are sometimes made worse by other phenothiazine derivatives or Rauwolfia alkaloids. It should also be suitable for treating patients with psychoneuroses and chronic brain syndrome."[6]

EVEN IN VERY SEVERE CASES "Of the 152 patients treated 25 have been released and they have not suffered a relapse. This proportion is significant if we stop to consider that we are dealing only with acute cases which had been considered hopeless and obviously destined to finish their days in an asylum."[7]

EXCELLENT THERAPEUTIC RESPONSE "Patients with emotional tensions resulting from the stress and strain of life . . . were treated with Mellaril at the dosage level of 10 mg. three times daily. In 94 such patients, 83 obtained an excellent therapeutic response."[8]



Mellaril®

THIORIDAZINE HCl

specific, effective tranquilizer • safer at all dosage levels



"... extremely satisfactory results ..."
in a clinical spectrum ranging from
minor nervous disorders to
severe psychotic disturbances[3]

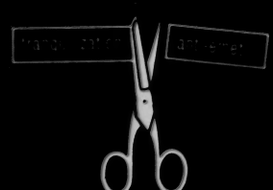
RESULTS WITH MELLARIL IN 194 PATIENTS[3]

ACUTE PSYCHOTICS	CHRONIC PSYCHOTICS	NEUROTICS
83% satisfactory effect	68% satisfactory effect	57% satisfactory effect
Some cases had complete remission of symptoms. Most were able to return home to useful occupations.	Relief of symptoms in cases permitted easier management and a return to a more or less useful life.	Some cases, complete relief of symptoms. Other cases, partial relief of symptoms.

RESULTS WITH MELLARIL IN PATIENTS PREVIOUSLY TREATED WITH OTHER TRANQUILIZERS[3]

DIAGNOSTIC CATEGORY	IMPROVED %	VERY SATISFACTORY %	SATISFACTORY %	UNSATISFACTORY %
SCHIZOPHRENIA				
Acute	89	61	28	11
Chronic paranoid	84.2	31.6	52.6	15.8
Chronic, other	73.9	21.7	52.2	26.1
Residual	57.1	9.5	47.6	42.9
CHRONIC BRAIN SYNDROME	66.6	33.3	33.3	33.3
CHRONIC PSYCHONEUROSIS	62.5	12.5	50	37.5
CHRONIC PSYCHOSOMATIC DISORDERS	75	25	50	25

Mellaril®



a guide to administration and dosage

Dosage ranges from 10 mg. three or four times a day in milder situations to 25 mg. three or four times a day for more disturbed patients. In ambulatory psychiatric out-patients, dosages of 50 to 100 mg. three or four times a day have been found adequate. For severely disturbed hospitalized psychotics, dosages of 200 to 300 mg. three times a day may be administered.

Dosage must be individualized according to the condition and degree of response. In all cases, the smallest effective dosage should be determined for each patient.

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
ADULTS		
Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneurosis, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
CHILDREN		
BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

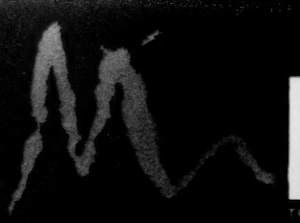
PRECAUTIONS: Although possessing a unique structure and a selectivity of action which broadens its therapeutic ratio, the physician should be alert to the possibility of untoward reactions in certain susceptible individuals. In particular, he should watch for potential hemopoietic depression, jaundice or orthostatic hypotension. As with other phenothiazines, Mellaril is contraindicated in severely depressed or comatose states from any cause.

SUPPLIED: MELLARIL Tablets, 10 mg., 25 mg., 100 mg. Bottles of 100.

1. Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. Kinross-Wright, V. J.: Lecture, Clinical Meeting, American Medical Association, Minneapolis, Dec. 4, 1958. 3. Kinross-Wright, V. J.: Scientific Exhibit, Clinical Meeting, American Medical Association, Minneapolis, Dec. 2-5, 1958. 4. Cohen, S.: TP-21, a new phenothiazine, Am. J. Psychiat. *115*:358, Oct. 1958. 5. Glueck, B.: Scientific Exhibit, American Psychiatric Association, Philadelphia, April 27-May 1, 1959. 6. Hollister, L. E., and Macdonald, B. F.: Presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959. 7. Remy, M.: Schweiz. med. Wchnschr. *88*:1221, Nov. 29, 1958. 8. Freed, S. C., in discussion on Thioridazine (Mellaril) in Psychiatric Patients, Hollister, L. E., and Macdonald, B. F., presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959.

- controls neurotic and psychotic patients with anxiety, apprehension, nervous tension
- virtual absence of jaundice, parkinsonism, photosensitivity, dermatitis
- minimal sedation and drowsiness
- does not mask organic conditions such as brain tumors, intestinal obstruction, etc., because of lack of anti-emetic action
- increased specificity of action results in greater safety at all dosage levels

SANDOZ



Mellaril®

THIORIDAZINE HCl

specific, effective tranquilizer • safer at all dosage levels



think of Terfonyl first

Squibb Triple Sulfas — Trisulfapyrimidines

THE TRIPLE SULFONAMIDE OF CHOICE IN COMMON URINARY, RESPIRATORY, AND OTHER BACTERIAL INFECTIONS



for effectiveness . . .
Prompt, high blood levels[1,2]
Excellent tissue diffusion[3]
Broad in scope—attacks both gram-positive and gram-negative pathogens[2,3]

for safety . . .
Highly soluble in urine—especially at critical pH levels[2]
Impressively low incidence of sensitization reactions[2,3]
Frequently avoids the problem of the development of resistant organisms

for economy . . .
Terfonyl is economical to prescribe for your patients

for palatability . . .
Good tasting, raspberry-flavored suspension appealing to all age groups—particularly the young and elderly patients

Supply:
Raspberry-flavored suspension, containing 0.167 Gm. each of sulfamethazine, sulfadiazine, and sulfamerazine per teaspoonful (5 cc.). Pint bottles.

Tablets, containing 0.167 Gm. each of sulfamethazine, sulfadiazine, and sulfamerazine per 0.5 Gm. tablet. Bottles of 100 and 1000.

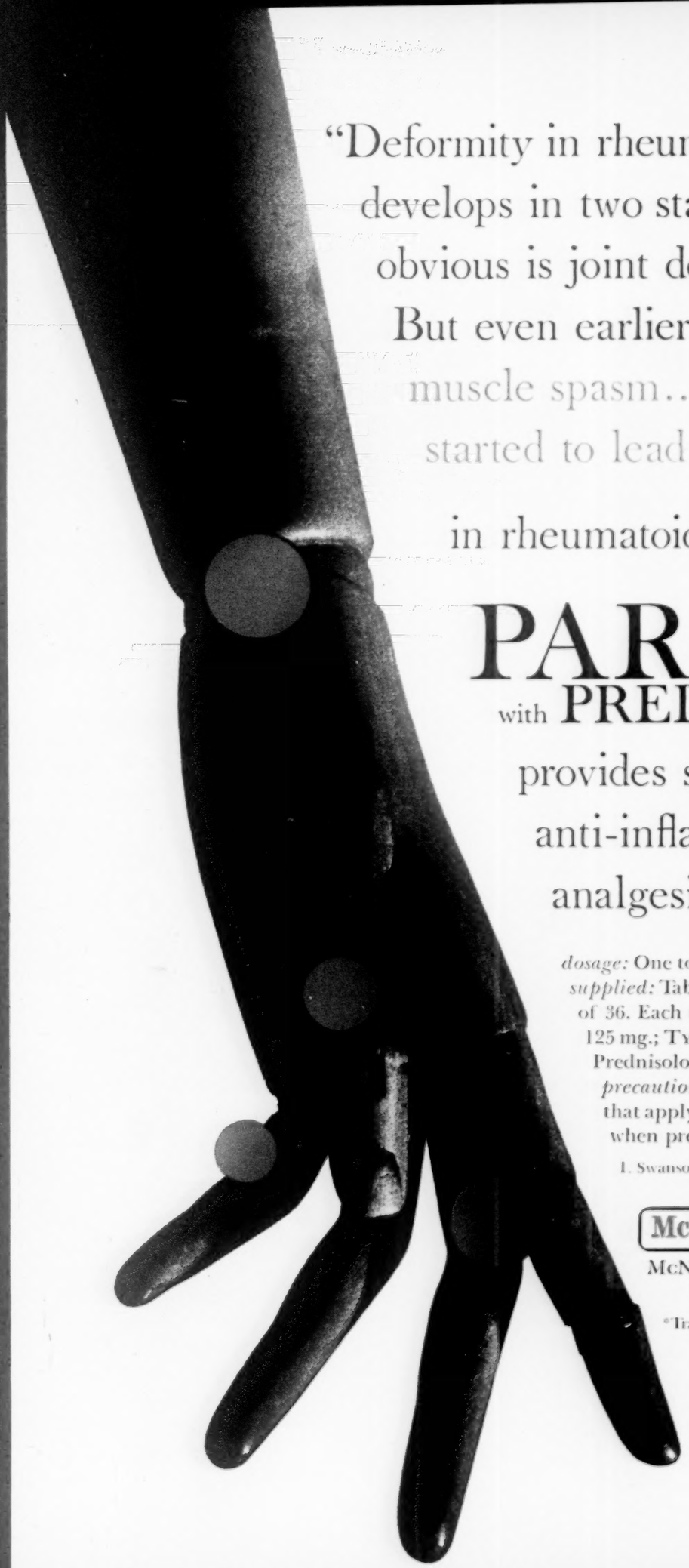
Also available:
Pentid-Sulfas: Each tablet contains 200,000 units of crystalline penicillin G potassium and 0.167 Gm. each of sulfamethazine, sulfadiazine, and sulfamerazine. Bottles of 30, 100 and 500.

References:
1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Company, 1957, p. 242. 2. Sophian, L. H.; Piper, D. L., and Schneller, G. H.: The Sulfapyrimidines, New York, A. Colish, 1952, pp. 70-76. 3. Lehr, D.: New York J. Med. 50:1361 (June 1) 1950.

SQUIBB

Squibb Quality / the Priceless Ingredient

"TERFONYL" AND "PENTIDS" ARE SQUIBB TRADEMARKS



"Deformity in rheumatoid arthritis develops in two stages. The most obvious is joint destruction. But even earlier... muscle spasm...has insidiously started to lead to deformity."[1]

in rheumatoid arthritis...

PARAFON*

with PREDNISOLONE

provides spasmolytic, anti-inflammatory, and analgesic action

dosage: One to two tablets three or four times a day.

supplied: Tablets, scored, buff colored, bottles of 36. Each tablet contains PARAFLEX® Chlorzoxazone† 125 mg.; TYLENOL® Acetaminophen 300 mg.; and Prednisolone 1.0 mg.

precautions: The precautions and contraindications that apply to all steroids should be kept in mind when prescribing PARAFON WITH PREDNISOLONE.

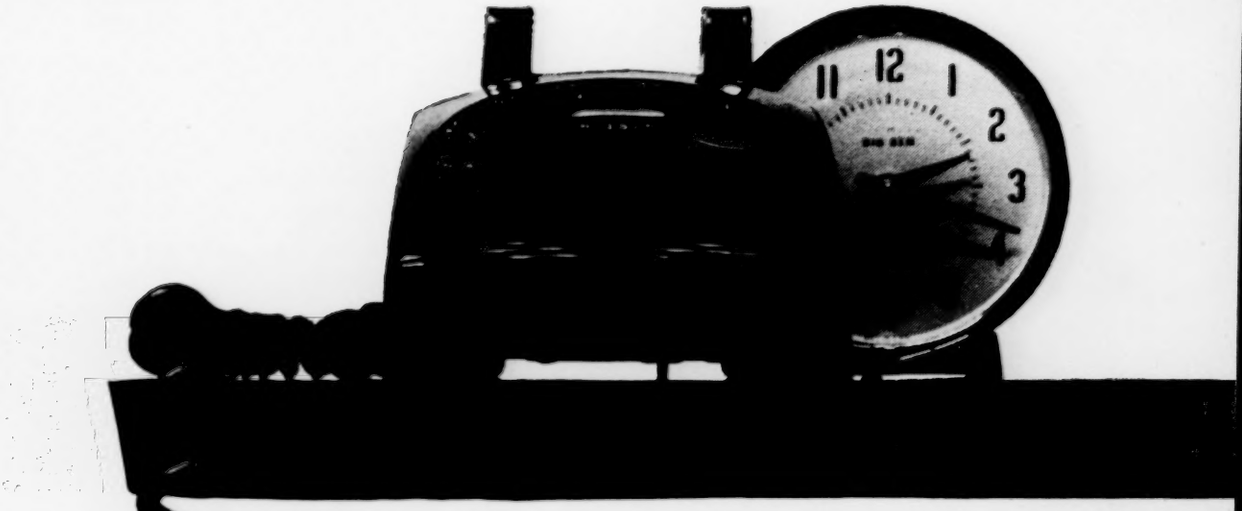
1. Swanson, J. N.: Canad. M. A. J. 79:638 (Oct. 15) 1958.

McNEIL

McNEIL LABORATORIES, INC • PHILADELPHIA 32, PA.

*Trade-mark †U.S. Patent Pending

265459



Emergency!

Phones are left to dangle when an acutely agitated patient creates an emergency situation.

The patient? Perhaps suffering postalcoholic syndrome—delirium tremens, for example. Or, a cardiac with intractable hiccups. Again, the patient might be a severely vomiting primigravida.

With SPARINE you are prepared for almost any crisis—psychic or physical. SPARINE helps control apprehension and agitation, nausea and vomiting, hiccups. It modifies reaction to pain and potentiates analgesics.

Sparine®

HYDROCHLORIDE
Promazine Hydrochloride, Wyeth

INJECTION TABLETS SYRUP

Wyeth®
Philadelphia 1, Pa.

GOUT

ANTURAN™

(sulfinpyrazone GEIGY)

High Potency Uricosuric Agent

By significantly increasing renal excretion of urate and thus lowering plasma uric acid, the new highly potent uricosuric agent ANTURAN strikes directly at the basic metabolic defect in gout.

Exceptionally high potency...4 to 6 times that of probenecid ...is the outstanding characteristic of ANTURAN. The effectiveness of ANTURAN is retained indefinitely and tolerance to it is good.

Clinically, ANTURAN:

- Prevents formation of new tophi
- Causes gradual absorption of old tophi
- Relieves chronic pain
- Restores joint mobility

ANTURAN is not designed for the treatment of acute attacks for which BUTAZOLIDIN is recommended. **Detailed Information On Request**

†Yü, T. F.; Burns, J. J., and Gutman, A. B. Arth. & Rheumat. 1:532, 1958

ANTURAN™ (sulfinpyrazone GEIGY). Scored tablets of 100 mg. in bottles of 100

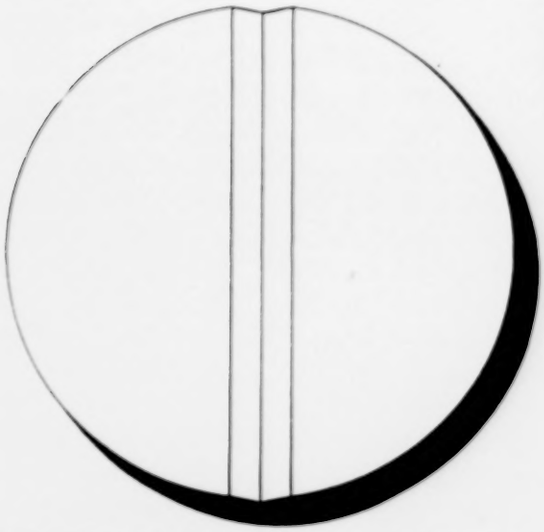
®BUTAZOLIDIN® (phenylbutazone GEIGY)

Ardsley, New York

GREATER CONVENIENCE

DOUBLE POTENCY

AT LOW COST TO YOUR PATIENT



Pentids '400'

Squibb 400,000 units Buffered Penicillin G Potassium Tablets

For the treatment of penicillin susceptible infections—ranging from mild to moderately severe—due to hemolytic streptococcus / pneumococcus / staphylococcus / and for the prevention of streptococcal infections where there is a history of rheumatic fever

Clinical effectiveness confirmed by millions of cases
Specific in many common infections
Daily dosage may be spaced without regard to mealtime
Ease of administration with oral penicillin
Economy for the patient

SQUIBB

Squibb Quality—the Priceless Ingredient

new convenient oral tablets

PENTIDS '400,' each scored tablet contains 400,000 units of penicillin G potassium buffered, bottles of 12 and 100. Twice the unitage of Pentids 200,000 units.

PENTIDS is a Squibb trademark.

also available

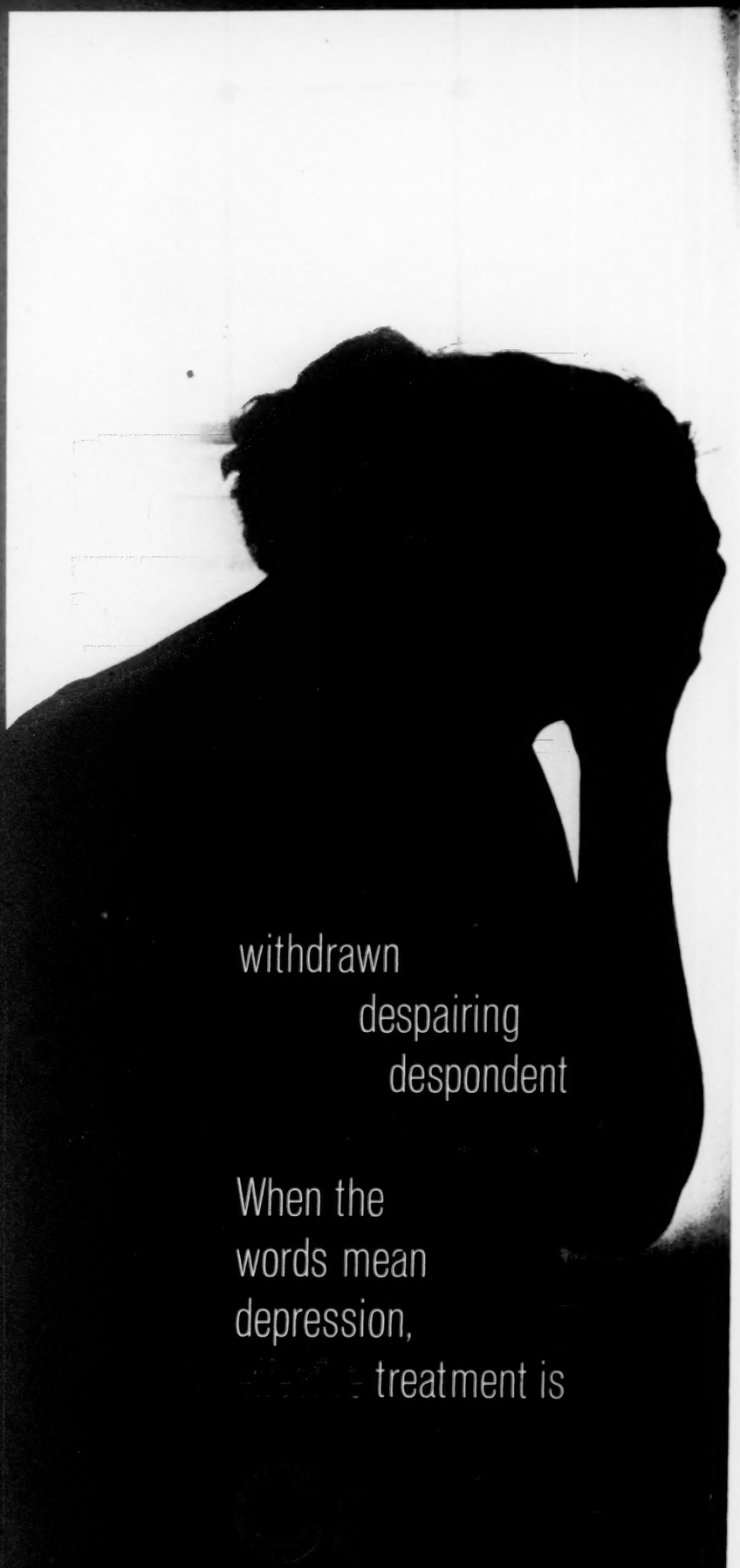
PENTIDS, 200,000 units of buffered penicillin G potassium per scored tablet, bottles of 12, 100, and 500.

PENTIDS FOR SYRUP, 200,000 units of penicillin G potassium per teaspoonful (5 cc.), 12 dose bottles.

PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 100, and 500.

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin G potassium per tablet, vials of 12 and bottles of 100.

PENTIDS-SULFAS TABLETS, 200,000 units of penicillin G potassium with 0.5 Gm. triple sulfas per tablet, bottles of 30, 100, and 500.



withdrawn
despairing
despondent

When the
words mean
depression,
treatment is

- revitalizes depressed patients[1-5]
- relieves pain in angina pectoris[6]
- lessens fatigue, aching, stiffness in rheumatoid arthritis[7]

HOW TO USE CATRON: CATRON Hydrochloride is a monoamine oxidase (MAO) inhibitor useful in the treatment of depression and of other disorders indicated below. It is recommended for use in carefully selected cases and in those patients who have not responded to the milder drugs.

ADMINISTRATION AND DOSAGE: Dosage of CATRON must be individualized according to each patient's response. The initial daily dose should not exceed 12 mg. and should be reduced as soon as the desired clinical effect is obtained. In severe depressions some clinicians desire rapid results and begin treatment with 24 mg. daily; this dosage should not be continued for more than a few days. A single daily dose in the morning is recommended. A continuous or interrupted schedule may be used, the latter during the maintenance period.

DEPRESSION (Endogenous, Reactive, Postpartum, Involutional and Depression Secondary to Schizophrenic or Neurotic Reaction): initially, 12 mg. once daily for approximately 2 weeks, or less if improvement appears. Dosage is then reduced to 6 mg. daily. As improvement continues, maintenance dosage of 6 mg. every other day or of 3 mg. daily often proves satisfactory. An interrupted dosage schedule is recommended for long-term therapy.

ANGINA PECTORIS: 3 to 6 mg. daily in most cases. Relief of pain and elevation of mood may be dramatic. Victims of angina pectoris who respond in this manner should be cautioned against overexertion induced by their sense of well-being.

RHEUMATOID ARTHRITIS (Adjunctive Therapy—in severely disabling forms, particularly when accompanied by depression): 9 to 12 mg. daily for 3 days, then 6 mg. daily, reducing further to 3 mg. daily on signs of improvement. If a conventional antiarthritic agent is used, lower doses of each are indicated.

CAUTION: Certain circumstances should be watched carefully when using CATRON.

DRUG POTENTIATION—The list of drugs which CATRON potentiates is not yet complete. CATRON should not be used concomitantly with any other drug unless, (a) it has been ascertained that the two drugs bear no qualitative relationship, or (b) potentiating action is being sought, as may be the case with tranquilizing drugs, including reserpine and the phenothiazines, and with the amphetamines, barbiturates and hypotensive agents.

HYPOTENSIVE EFFECT—All normotensive patients receiving CATRON, but especially elderly patients, should be warned about the possibility of orthostatic hypotension during the initial period of higher dosage. In the few instances where this may occur, lowering of the dose will usually permit continuation of therapy.

COLOR VISION—A reversible red-green color defect has been reported in a few patients, chiefly hypertensives, on extended therapy with CATRON. Discontinue the drug if such changes occur.

For detailed information, request brochure No. 19, CATRON

Catron®

β-phenylisopropyl hydrazine supplied as the hydrochloride

important new psychoactive agent

ANIMALS, NEUROLOGIC SIGNS—In toxicity studies with animals, a neurologic syndrome has been observed characterized by tremors, muscle rigidity and difficulty in locomotion. Although extensive clinical experience has not shown such reactions to be a problem in humans in recommended dosage, should a similar neurologic disturbance occur, the possibility of drug action should be considered.

SIDE EFFECTS—Major side effects requiring cessation of therapy are infrequent. Other side effects—constipation, delay in starting micturition, increased sweating, hyperreflexia, ankle edema, blurring of vision, dryness of the mouth—are usually readily controlled by lowering the dosage. Rash, observed in a few patients, cleared up rapidly upon discontinuing therapy.

WARNING: Pharmacologic studies show that with proper dosage CATRON will inhibit monoamine oxidase in the brain without influencing this enzyme in the liver. This is in contrast to previous inhibitors which depress monoamine oxidase activity in the liver before affecting this enzyme in the brain.
Although the evidence suggests that serious life-threatening hepatitis seen with other MAO inhibitors should not occur with CATRON in the recommended dosage, it has been reported on rare occasion with dosages in excess of the recommended levels.

The Following Precautions Are Recommended:

1. In all instances daily dose should not exceed 12 mg.
2. Reduce daily dose as soon as response is established, usually in a matter of 1 to 2 weeks.
3. Do not prescribe to a patient more than sixteen 6 mg. tablets or thirty-two 3 mg. tablets of CATRON at one time.
4. Patients should return for observation before additional CATRON is prescribed. For this reason, prescriptions for CATRON should be marked "not refillable."
5. Perform regular liver function tests.
6. Do not use the drug in patients with a history of viral hepatitis or other liver abnormalities.

CATRON is the original brand of β-phenylisopropyl hydrazine. It is supplied as the hydrochloride in tablets of 3 mg. and 6 mg., bottles of 50.

REFERENCES (1) Agin, H. V.: A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, in press. (2) **Ibid.**: The Use of JB-516 (CATRON) in Psychiatry, Conference on Amine Oxidase Inhibitors, New York Acad. Sc., Nov. 20-22, 1958. (3) Bercel, N. A.: **op. cit.** (ref. 1). (4) Kinross-Wright, J.: Panel Discussion of Psychic Energizers, **op. cit.** (ref. 1). (5) Kinross-Wright, J.: Experience with JB-516 (CATRON) and other Psychochemicals in Clinical Practice, Conference on Amine Oxidase Inhibitors, New York Acad. Sc., Nov. 20-22, 1958. (6) Kennamer, R., and Prinzmetal, M.: Treatment of Angina Pectoris with CATRON (JB-516), Am. J. Cardiol. 3:542, 1959. (7) Scherbel, A. L., and Harrison, J. W.: The Effects of Iproniazid and Some Other Amine Oxidase Inhibitors in Rheumatoid Arthritis, Conference on Amine Oxidase Inhibitors, New York Acad. Sc., Nov. 20-22, 1958.

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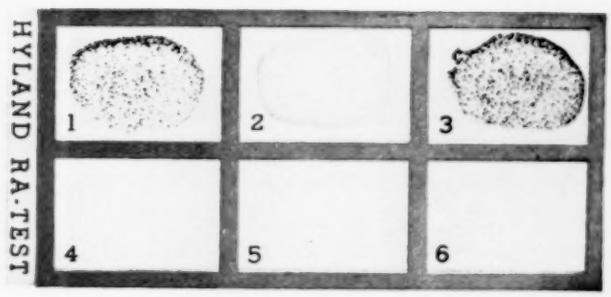
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A FAST, SIMPLE, RELIABLE
SCREENING TEST FOR
RHEUMATOID ARTHRITIS

a rapid slide modification of the latex fixation test

RA-TEST®



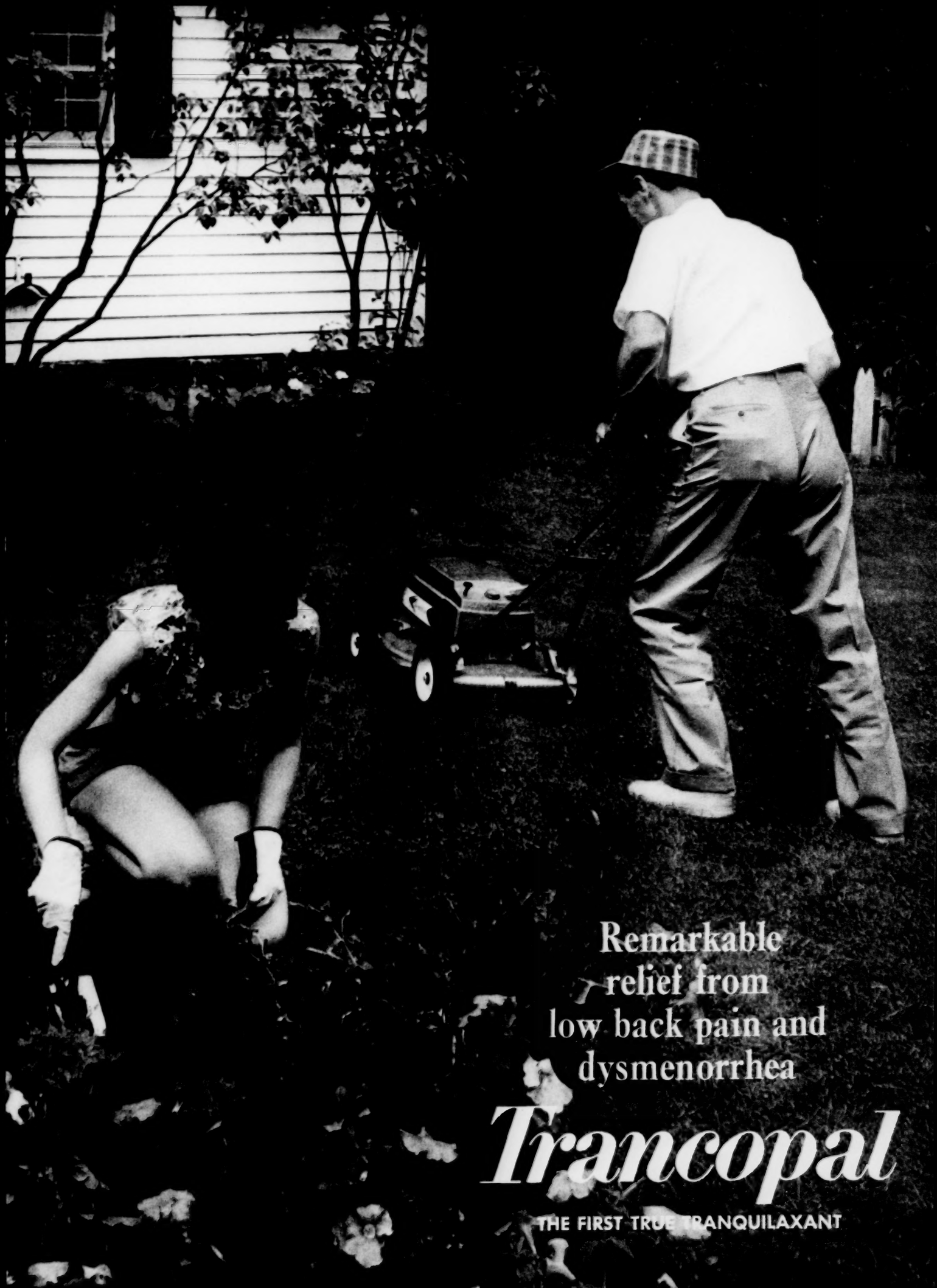
EASY TO PERFORM—just mix separate drops of Latex-Globulin Reagent with: (1) patient's diluted serum, (2) Negative Control Serum, and (3) Positive Control Serum on divided areas of slide.

EASY TO READ—positive reactions (indicating presence of rheumatoid factor) are clearly visible to the naked eye in a few seconds. Negative tests remain smooth, with no visible clumping.

SUPPLIED—in compact kits containing 5 cc. Latex-Globulin Reagent, 2 cc. Positive Control Serum, 2 cc. Negative Control Serum, 100 cc. Glycine-Saline Buffer Diluent, and divided glass slide. Each kit sufficient for at least 100 tests. Test components are also available separately.

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relief from
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dysmenorrhea
Trancopal
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for low back pain

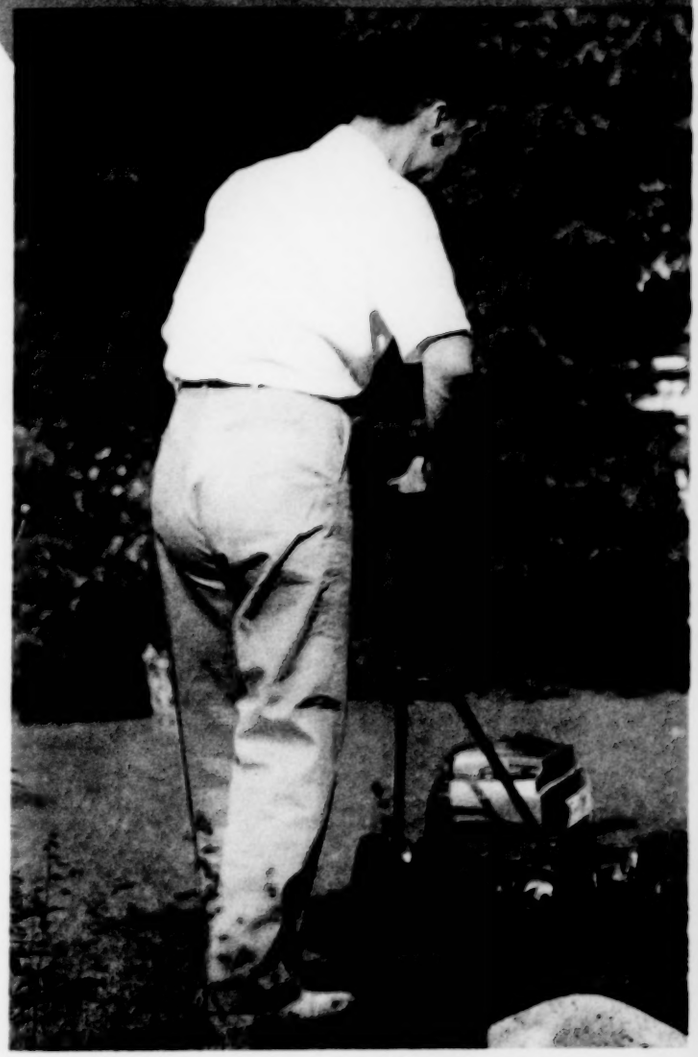
case profile no. 2758*

A middle-aged man had intermittent low back pain attributed to injuries received in an automobile accident three years ago. The pain radiated down both legs, making the patient walk bent over. He also had difficulty in getting out of bed and had to pull his knees up and roll out. Any heavy lifting precipitated a new attack, and he tired easily.

Findings on x-ray of the thoracic and lumbar spine were negative. All other laboratory studies were within normal limits. A herniated disc, though still a possibility, was temporarily ruled out by the neurologic examination. Previous treatment consisted of analgesics, steroids (without success), and narcotics during severe attacks.

On a dosage of Trancopal, 100 mg. t.i.d., this patient is able to walk around almost normally and carry on his regular activities as long as he does not overdo. He has received Trancopal for over seven months with excellent relief of symptoms. There have been no side effects.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*



what you
when you

THE FIRST TRUE TRANQUILAXANT

Trancopal®



for dysmenorrhea
and premenstrual tension

case profile no. 3347*

A 35-year-old housewife had a history of severe dysmenorrhea and premenstrual tension. Menarche occurred at the age of 14. She is a gravida 2, para 1. Her menstrual cycle is fairly regular, and previous medical history indicates no apparent abnormalities. Findings on pelvic examination were negative. Severe tension and irritability routinely occurred from two to seven days before and during menstruation. Cramping was experienced for all three days of the menstrual period. Analgesic preparations provided limited symptomatic relief.

Trancopal, 200 mg. t.i.d., was prescribed for dysmenorrhea. It not only has relieved the severe cramping, but has provided a welcome relief from the irritability accompanying it. Because of these excellent results, Trancopal also was prescribed for her tenseness during the premenstrual period with a most gratifying response.

This patient has successfully remained on the above regimen for over six months without adverse effects.

Turn Page for Complete Listing of Indications and Dosage

THE FIRST TRUE TRANQUILAXANT

Trancopal

potent muscle relaxant

effective tranquilizer

- In musculoskeletal disorders, effective in 91% of patients.[1]
- In anxiety and tension states, effective in 88% of patients.[1]
- Low incidence of side effects (2.3% of patients). Blood pressure, pulse rate, respiration and digestive processes unaffected by therapeutic dosage. No effects on hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

Indications:

Musculoskeletal:
Low back pain (lumbago, etc.)
Neck pain (torticollis, etc.)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disc syndrome
Fibrositis
Ankle sprain, tennis elbow, etc.
Myositis
Postoperative muscle spasm

Psychogenic:
Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris
Alcoholism

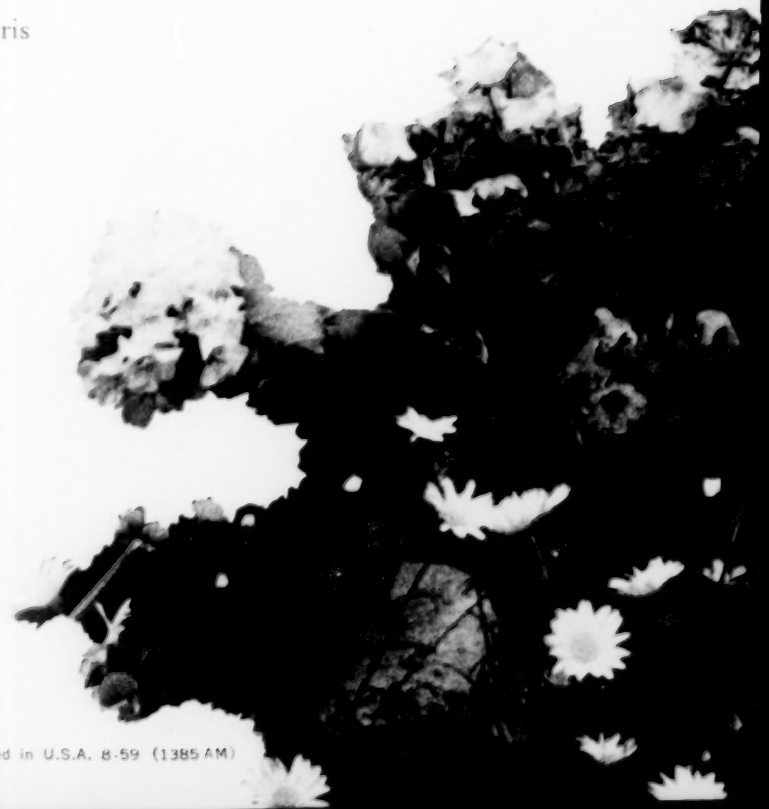
Now available in two strengths:

Trancopal Caplets®:
100 mg. (peach colored, scored), bottles of 100.

New Strength ▶ Trancopal Caplets:
200 mg. (green colored, scored), bottles of 100.

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours.

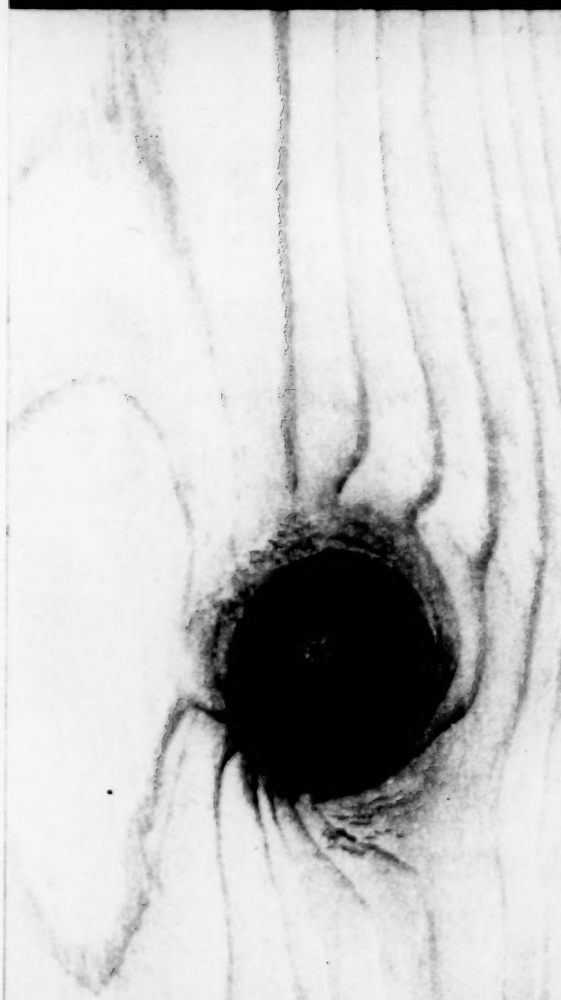
1. Collective Study, Department of Medical Research, Winthrop Laboratories.



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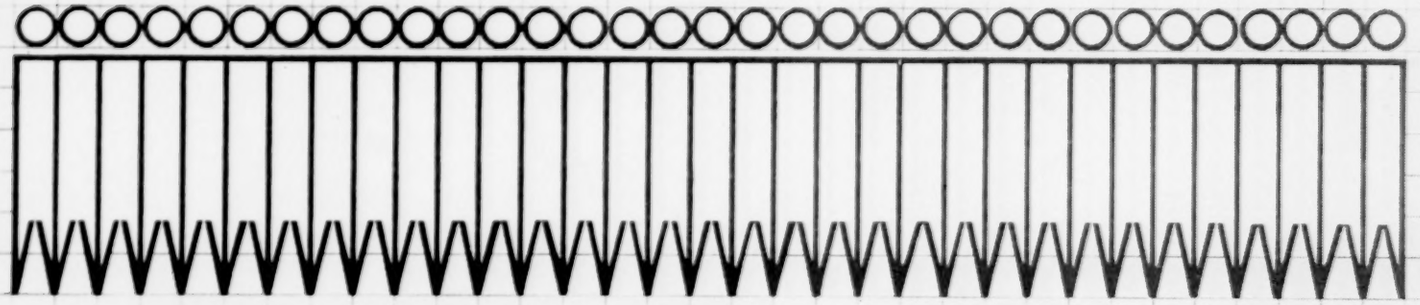
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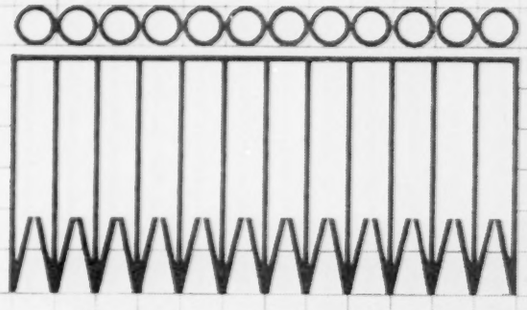
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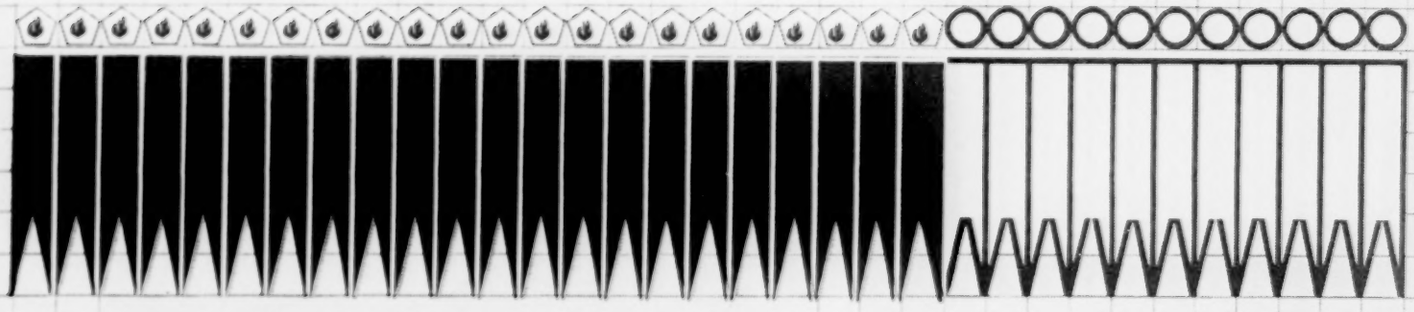
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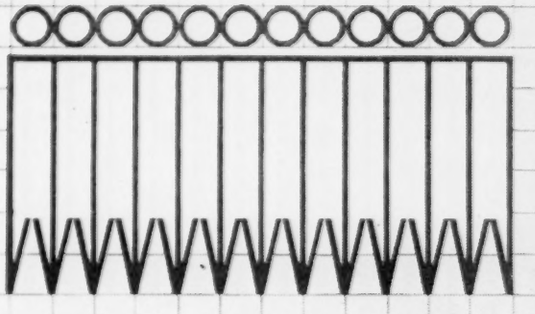


Of 45 arthritic patients
who were refractory
to other corticosteroids*





22 were successfully
treated with **Decadron**[1,2]



1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

*Cortisone, prednisone and prednisolone.

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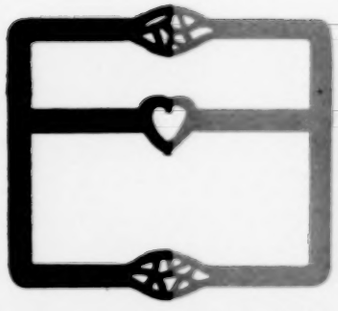
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REFERENCES: 1. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: New England J. Med. 260:872 (April 23) 1959. 2. Fuchs, M.; Bodi, T., and Moyer, J. H.: Am. J. Cardiol. 3:676 (May) 1959. 3. Fuchs, M., and others: Monographs on Therapy 4:43 (April) 1959. 4. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: Am. Heart J. 57:484 (April) 1959. 5. Rochelle, J. B., III; Montero, A. C., and Ford, R. V.: Antibiotic Med. & Clin. Ther. 6:267 (May) 1959. LITERATURE AVAILABLE ON REQUEST

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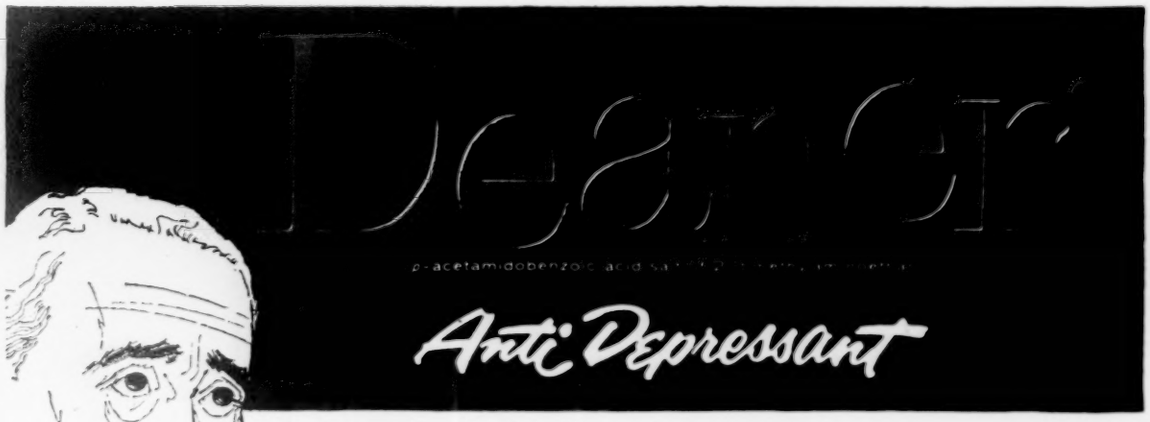
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References: 1. Graham, W.: Canad. M. A. J. **79**:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. **8**:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugier, W. E., and Champlin, B. M.: New England J. Med. **256**:388, 1957.

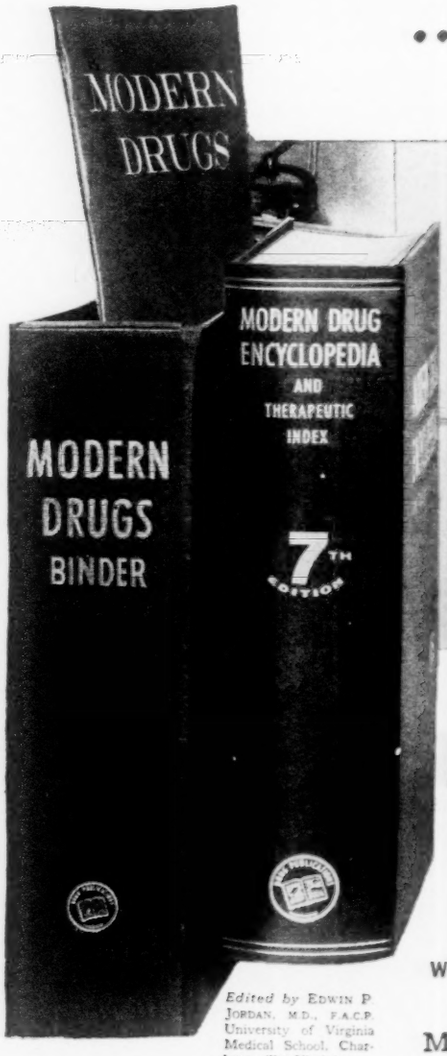
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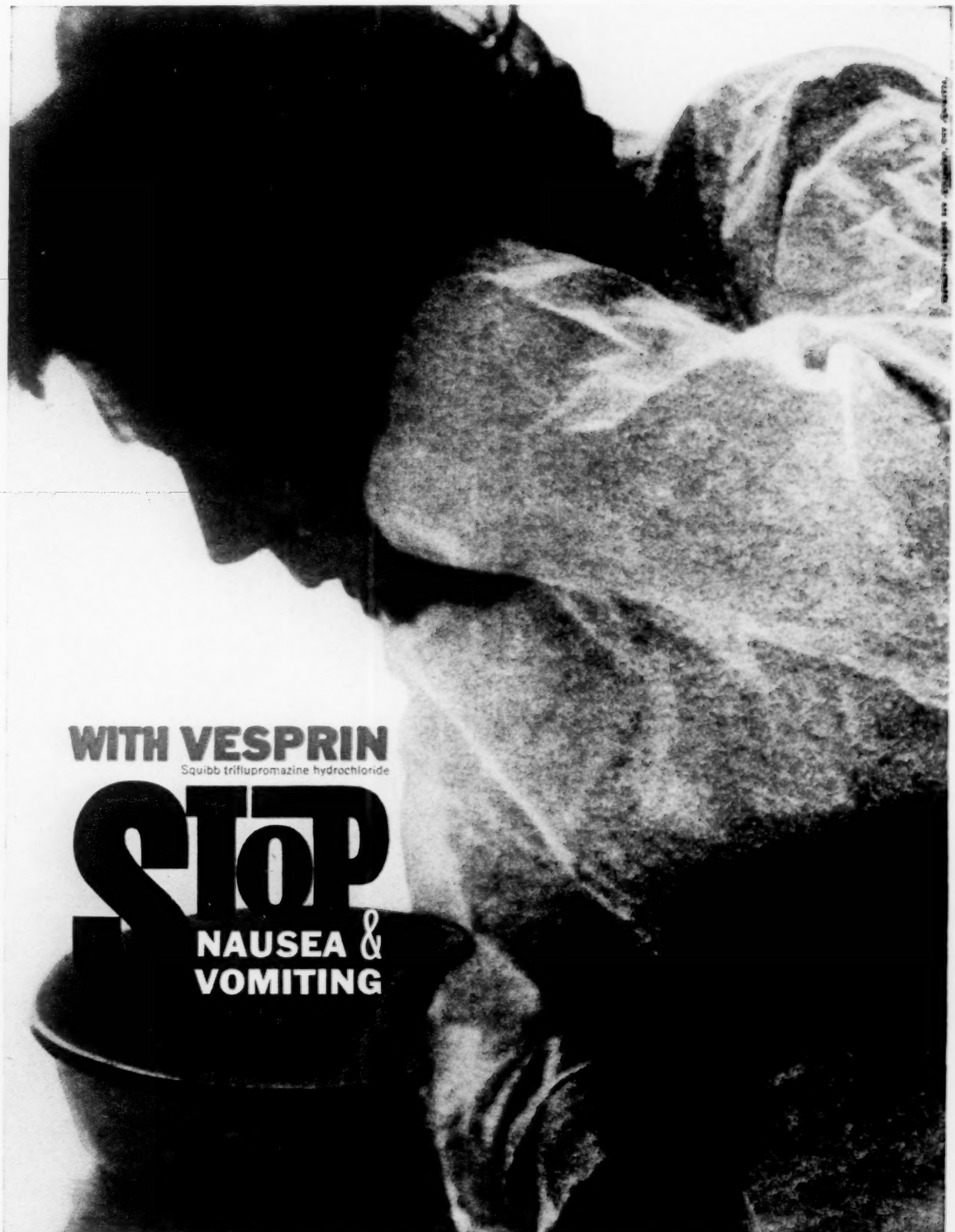
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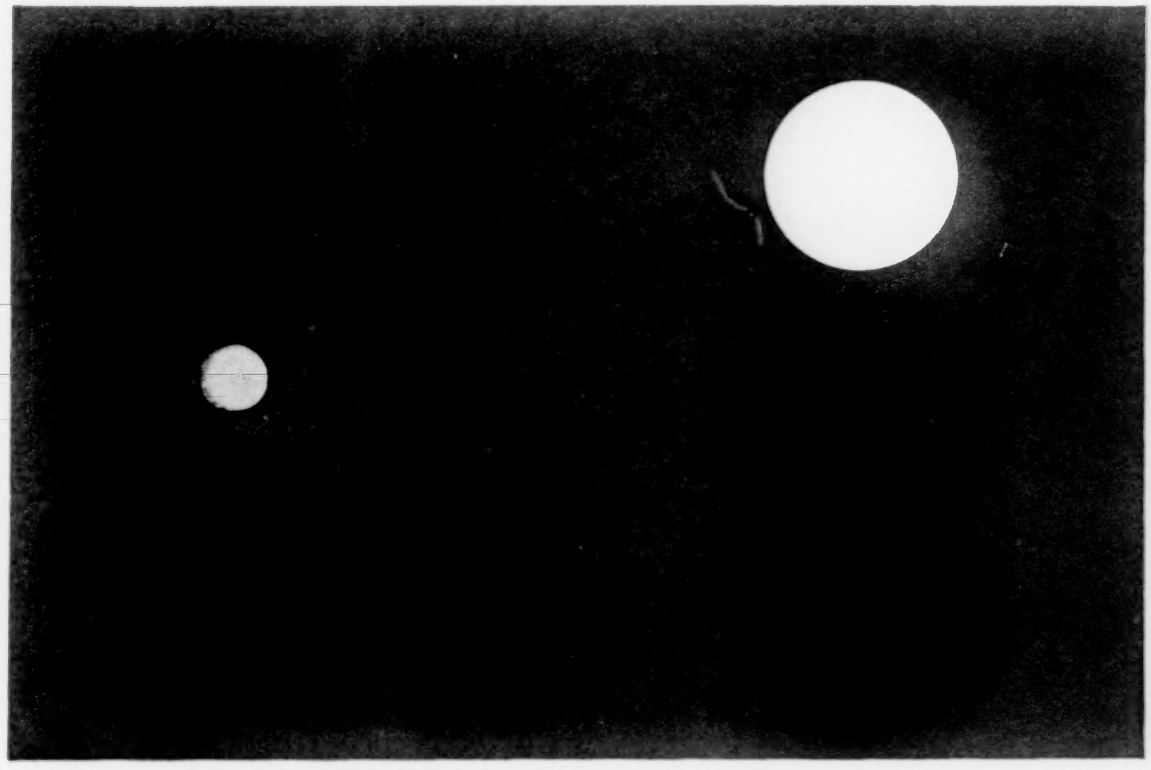
References: 1. M. M. Fisher and H. E. Tebrock: *New York State J. Med. 53*:65, 1953. 2. R. O. Gilhespy: *Brit. M. J. 1*:207, 1957. 3. E. C. Texter, et al.: *Am. J. Med. Sc. 224*:408, 1952. 4. W. Redisch and O. Brandman: *Angiology 1*:312, 1950. **Complete bibliography available on request.**

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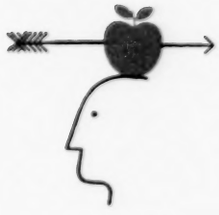
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1. Neustadt, D. H.: Corticosteroid Therapy in Rheumatoid Arthritis: Comparative Study of Effects of Prednisone and Prednisolone, Methylprednisolone, Triamcinolone and Dexamethasone, J.A.M.A. 170:1253 (July 11) 1959.

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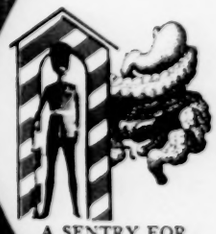
SUMMARY OF CASES

Clinical Diagnosis	*Oxyphencyclimine[1,2,3,5]	†ENARAX[2,5]
Peptic ulcer	440	48
Gastritis	16	17
Gastroenteritis	—	55
Colitis	37	—
Duodenitis	6	3
Functional bowel syndrome	14	—
Hiatus hernia (symptomatic)	16	1
Pylorospasm or cardiospasm	11	2
Irritable bowel	11	—
Biliary tract dysfunctions	11	1
Miscellaneous	7	29
Total number of patients	569	156
Clinical Results *Excellent*	445	150
Fair	56	—
Failure	68	6

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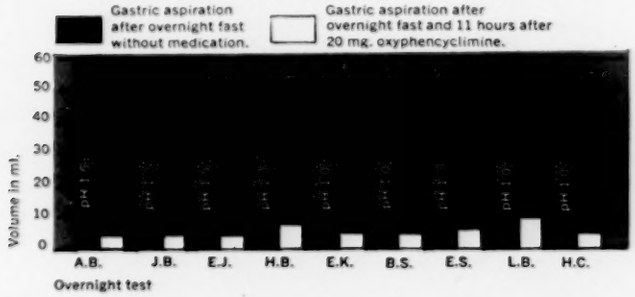
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References: 1. Winkelstein, A.: Am. J. Gastroenterol., in press. 2. Leming, B. H., Jr.: Clin. Med. 6:423 (March) 1959. 3. McHardy, G., et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, Calif., January 27, 1958. 4. Strub, I. H., and Carballo, A.: To be published. 5. Data in Roerig Medical Department files. 6. Steigmann, F.: To be published. 7. Schuller, E.: Gaz. des Hôpitaux *10*:391 (Apr. 10) 1937. 8. Farah, L.: Internat. Rec. Med. *169*:379 (June) 1956. 9. Harrisson, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957.

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"rescinnamine has less slowing effect on the heart than does reserpine and apparently has less gastrointestinal effect."[2]

"the addition of rescinnamine reduced the need for high doses of ganglion-blocking agents."[1]

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MODERIL BIBLIOGRAPHY 1. Winton, S. S.: Internat. Rec. Med. 170:665, 1957. 2. Hershberger, R. L.; Dennis, E. W., and Moyer, J. H.: Am. J. M. Sc. 231:542, 1956. 3. Moyer, J. H.: A. M. A. Arch. Int. Med. 96:518, 1955. 4. Moyer, J. H.; Dennis, E., and Ford, R.: Ibid. p. 530. 5. Council on Drugs, A. M. A.: New and Nonofficial Drugs 1959, Philadelphia, Lippincott, 1959, p. 374. 6. Smirk, F. H.: Postgrad. Med. 25:11, 1959. 7. Moyer, J. H., et al.: South. M. J. 50:499, 1957. 8. Malamud, W., et al.: Am. J. Psychiat. 114:193, 1957. 9. Smirk, F. H., and McQueen, E. G.: Lancet 2:115, 1955. 10. Malitz, S.: J. Chron. Dis. 9:278, 1959.

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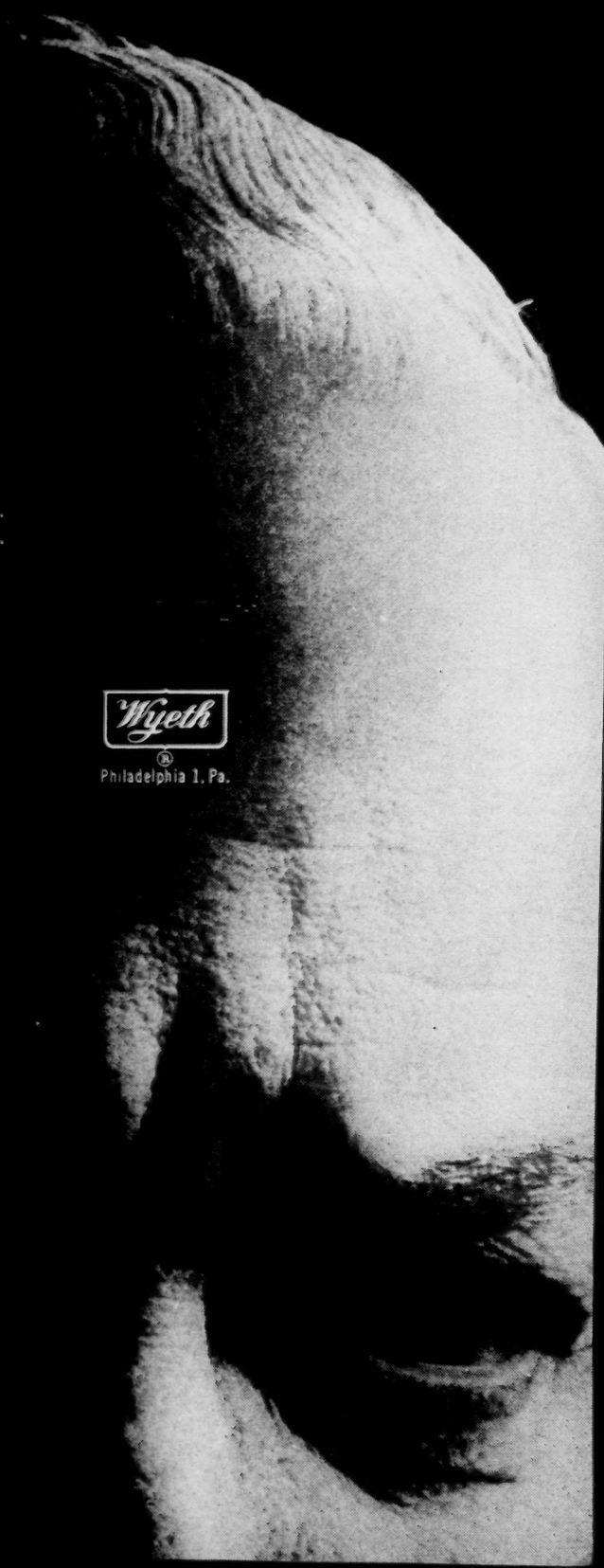
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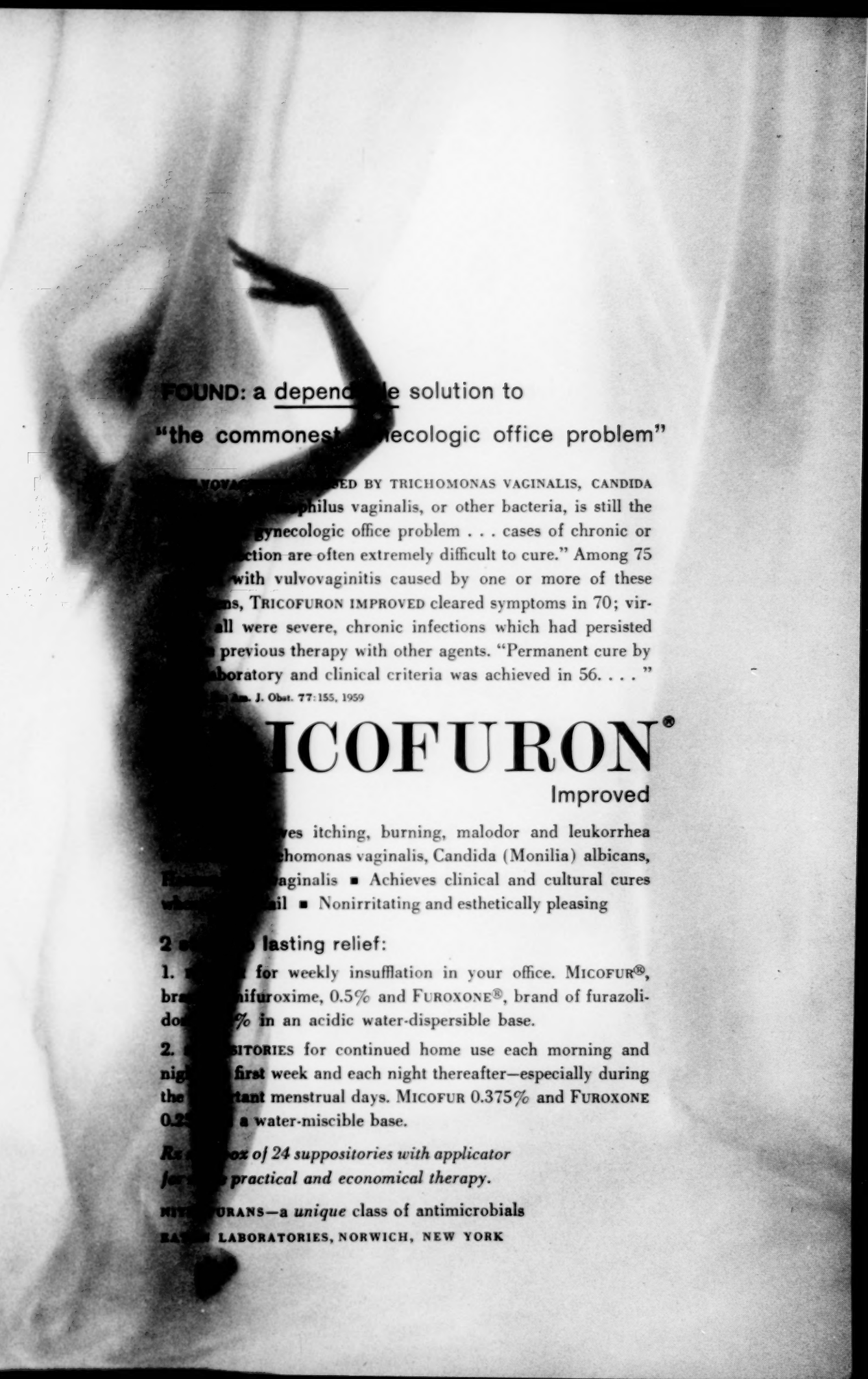
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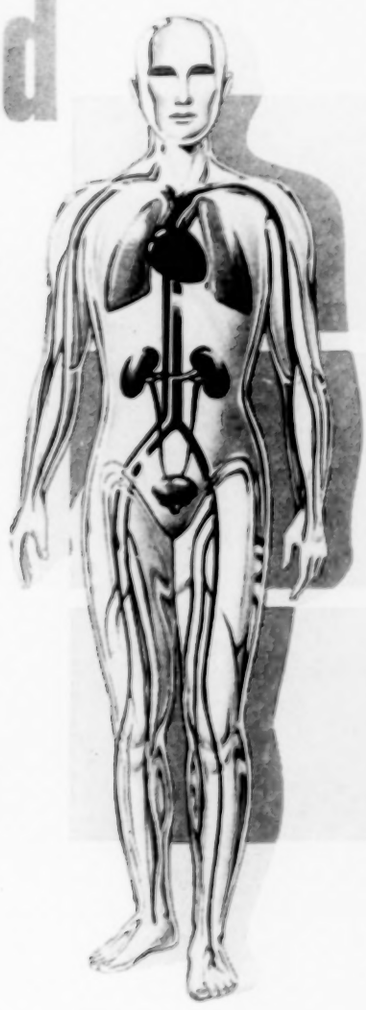
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In approximately 70% of cases, Marplan

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1. What is Marplan? Marplan is a hydrazine derivative with marked potency in regulating the amine oxidase enzyme system. Already evaluated in over 3500 patients, Marplan has demonstrated marked beneficial effects in the treatment of angina pectoris. Evidence to date indicates that Marplan may also be therapeutically valuable in a number of other important acute and chronic medical conditions. Chemically, Marplan is 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine.

2. What is the effect of Marplan in angina pectoris? Continued prophylactic administration of Marplan provides symptomatic relief—in the form of pain control and reduced nitroglycerin requirements—in approximately 70 per cent of cases.[1-3] "Excellent effects with relatively small doses" are reported in a group of 31 patients with angina pectoris. In that study, Marplan "afforded greater relief than any other compound in our experience."[3] To date, Marplan prophylaxis has been evaluated in a total of 238 anginal cases. The response rate was 72.7 per cent, with improvement ranging from a reduction in the number of attacks to virtual abolition of the anginal state.[1]

3. What is the effect of Marplan on blood pressure? Marplan should not be used as a hypotensive agent. The possibility of postural hypotension, though relatively infrequent, must be borne in mind.

4. What type of angina case is particularly responsive to Marplan prophylaxis? Marplan has been evaluated in angina of varying severity. It is felt, however, that optimum benefit will be derived in moderately severe to intractable cases.

5. Is the antianginal effect of Marplan the same as its antidepressant action? Marplan is unique in that it exhibits two distinct primary effects: its antianginal action, while biochemically related, is clinically separate from its antidepressive effects.

6. How can one compound have two such seemingly dissimilar effects? The mechanism of action of Marplan and of the other amine oxidase regulators is not yet fully defined. Marplan's pharmacologic effects are secured indirectly: By regulating amine oxidase levels; it inhibits the breakdown of serotonin, norepinephrine and other biologically active amines. In animal experiments, serotonin infusion of the heart muscle produces an increase in the ratio of coronary blood flow to coronary vascular resistance.[4]

questions define the scope of prophylaxis in angina pectoris

7. How should Marplan be given? The usual starting dose is 30 mg daily to be given in single or divided doses. The patient should be observed carefully and individual dosage adjustment made according to response. Many patients will respond quickly to the initial dose of 30 mg daily, and the dosage should then be reduced to 10 or 20 mg daily (or less) for maintenance therapy. In some patients beneficial effects may not be observed for three or four weeks. Since daily doses larger than 30 mg may cause an increase in side effects, such as hypotension and constipation, it is not recommended that higher dosages be employed.

8. What are the precautions? All patients treated with hydrazine derivatives should be kept under close medical supervision. While there is no definite knowledge of a hazard with Marplan, use of this class of agent should be discontinued at the first sign of jaundice or impaired liver function. Periodic liver function tests are advised during hydrazine therapy. These drugs are contraindicated in patients with a history of previous liver disease or impaired liver function. In patients with impaired kidney function, Marplan should be used cautiously to prevent accumulation and should not be used in epileptic patients. Patients receiving a hydrazine in conjunction with drugs such as alcohol, ether, barbiturates, meperidine, cocaine, procaine, and phenylephrine should be more closely supervised.

9. What are the side effects, if any? In one of the largest bodies of clinical material for this new class of drugs, Marplan shows one of the lowest recorded incidences of side effects. Particular attention was focused on attempts to define as precisely as possible amine oxidase inhibitor side effects on a wide range of organs, including liver and bone marrow. Extensive clinical studies have revealed no jaundice or liver damage attributable to Marplan. Nevertheless, since Marplan is an amine oxidase inhibitor, the same precautions should be observed with Marplan therapy as with other amine oxidase inhibitors. Since Marplan is a potent therapeutic agent affecting many enzyme systems of the body, side effects may be expected to occur in a certain percentage of cases. Side effects have rarely been severe enough to necessitate discontinuance of Marplan therapy. However, as with all agents of this type, the patient should be observed for signs of orthostatic hypotension, complaints of dizziness and vertigo, constipation, overactivity, jitteriness, insomnia, peripheral edema, weakness, fatigue, dryness of the mouth, blurred vision and skin rashes.

10. How can patients be transferred from their present anginal prophylaxis? Initially the established nitrite regimen should be maintained, while simultaneously placing the patient on a daily dose of 30 mg Marplan. The patient is to be observed carefully and nitrite intake decreased as pain episodes diminish. Response to Marplan prophylaxis may be delayed for several weeks.

Marplan

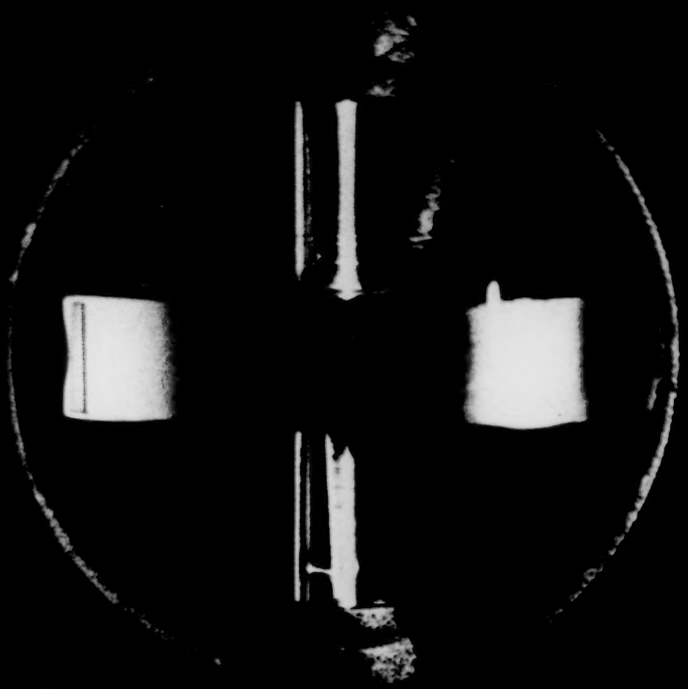
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References: 1. Clinical reports on file, Roche Laboratories. 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. 3. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. C. W. Crumpton, et al., Conference on Amine Oxidase Inhibitors, New York City, November 20-22, 1958.

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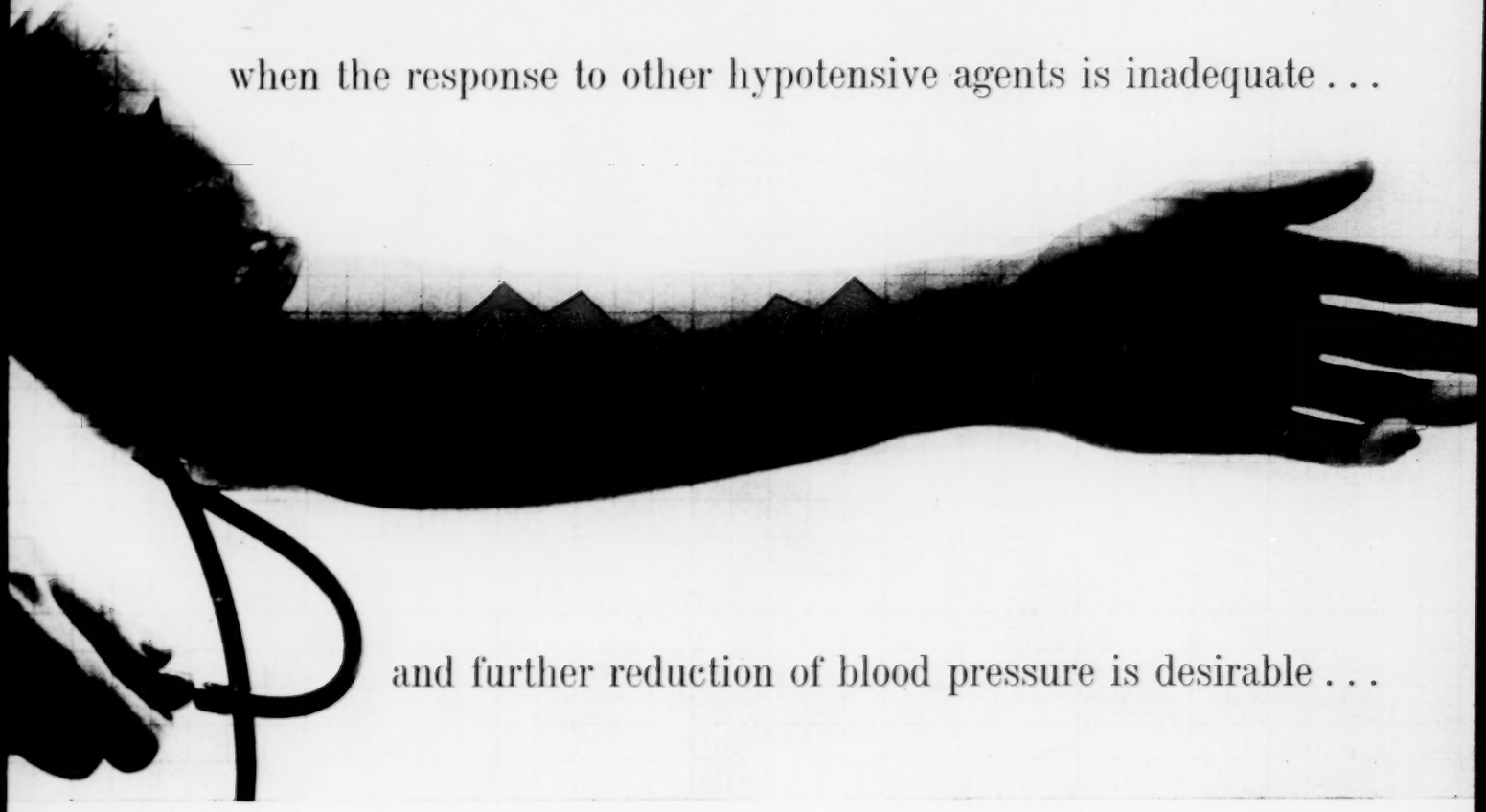
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A.M.A. Council on Drugs, New and Nonofficial Drugs: Philadelphia, J. B. Lippincott Co., 1958, p. 285

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Beem, J. R., and Moyer, J. H.: Geriatrics 13:375, June 1958

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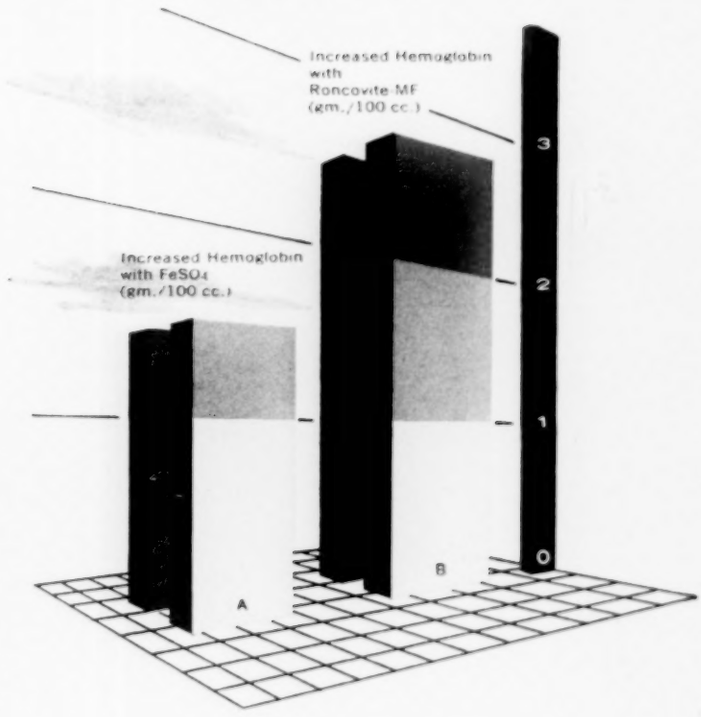
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(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood *13*:55 (Jan.) 1958. (2) Gurney, C. W.; Jacobson, L. O., and Goldwasser, E.: Ann. Int. Med. *49*:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C., and Bethell, F. H.: J. Lab. & Clin. Med. *52*:364 (Sept.) 1958. (4) Ausman, D. C.: Journal-Lancet *76*:290 (Oct.) 1956. (5) Holly, R. G.: Obst. & Gynec. *9*:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec. *1*:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinois M. J. *113*:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas J. Med. *51*:686 (Oct.) 1955.

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